FDAAC

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8:00 AM ET

Julia Johnson:	Good morning. I would first like to remind everyone present to please silence their cell phones, Blackberrys, any other device if you have not done so already. I would like to identify the FDA press contacts, Dr. Jeff Ventura. If you're here, could us stand, Jeff? That's okay. We'll move ahead. Good morning, my name is Julia Johnson. I'm the Acting Chair of the Advisory Committee for Reproductive Health Drugs. I will now call the joint meeting of the advisory for Reproductive Health Drugs and Drug Safety, and Risk Management Advisory Committee to order. We will go around the room and please introduce yourself. We will start with FDA and Dr. Julie Beitz is on my left and we'll go around the table from there. Dr. Bietz?
Julie Beitz:	Good morning. My name is Julie Beitz. I'm the Director of the Office of Drug Evaluation III.
Scott Monroe:	I'm Scott Monroe, Director of the Division of Reproductive and Urologic Products.
Lisa Soule:	I'm Lisa Soule, Clinical Team Leader in the Division of Reproductive and Urologic Products.
Gerald Dal Pan:	Good morning. I'm Gerald Dal Pan, Acting Director of the Office of Surveillance and Epidemiology.
Judy Staffa:	Judy Staffa, Director of Division of Epidemiology II and the Office of Surveillance and Epidemiology.
Rita Ouellet-Hellstrom:	Rita Ouellet-Hellstrom, Associate Director for Science, Division of Epidemiology.
Eve Espey:	I'm Eve Espey, Professor of OB/GYN at the University of New Mexico.
Geri Hewitt:	I'm Geri Hewitt of the Ohio State University.
Paula Hillard:	Paula Hillard, Professor of Obstetrics and Gynecology at Stanford University Medical Center.
Dale Stovall:	Dale Stovall. Reproductive Endocrinologist, University of Virginia.

Diane Aronson:	Diane Aronson, Patient Representative, Cambridge, Massachusetts.
Bart Clarke:	Bart Clarke. Adult Endocrinology from Mayo Clinic.
Melissa Gilliam:	Melissa Gilliam, Professor of OB/GYN, the University of Chicago.
John Kittelson:	John Kittelson, Professor of Biostatistics at the University of Colorado, Denver.
Kathleen Hoeger:	Kathleen Hoeger, Professor of Obstetrics and Gynecology, University of Rochester.
Michele Orza:	Michelle Orza, Analyst with the National Health Policy Forum.
Julia Johnson:	Julia Johnson. I'm Professor and Chair of OB/GYN, University of Massachusetts.
Kalyani Bhatt:	Good morning. I'm Kalyani Bhatt. I'm the Designated Federal Officer.
Valerie Montgomery Rice:	Good morning. Valerie Montgomery Rice, Morehouse School of Medicine.
Mark Woods:	Mark Woods. I'm the Clinical Coordinator and Residency Program Director in the pharmacy at St. Luke's Hospital in Kansas City.
Elaine Morrato:	Good morning. Elaine Morrato from the Colorado School of Public Health in the Department of Health Systems Management and Policy.
Peter Kaboli:	I'm Peter Kaboli. I'm a General Internist from the University of Iowa and the Iowa City CVA.
Almut Winterstein:	Good morning. Almut Winterstein. I'm Associate Professor in Pharmaceutical Outcomes and Policy at the College of Pharmacy and in Epidemiology at the Colleges of Medicine and Public Health at the University of Florida.
Sid Wolfe:	Sid Wolfe. I'm an Internist and Director of the Health Research Group at Public Citizen.
Sonia Hernandez-Diaz:	Sonia Hernandez-Diaz, Associate Professor of Epidemiology, Harvard School of Public Health in Boston.
Maria Suarez-Almazor:	Good morning. Maria Suarez-Almazor, Professor of Medicine, University of Texas, M.D. Anderson Cancer Center.
Bob Wild:	Good morning. Bob Wild, University of Oklahoma Health Science Center and Professor of OB/GYN and Reproductive Epidemiology and Biostatistics.
Naomi Tepper:	Naomi Tepper. I'm an OB/GYN in the Division of Reproductive Health from CDC.
Jacqueline Gardner:	Jacqueline Gardner, University of Washington, School of Pharmacy.
Sean Hennessey:	Good morning. My name is Sean Hennessey. I do pharmacoepidemiology research at the University of Pennsylvania.
Enrique Schisterman:	Good morning. I'm Enrique Schisterman. I'm a Branch Chief of the epidemiology branch at NICHD.

Elizabeth Raymond: Elizabeth Raymond, Senior Medical Associate from Gynuity Health Projects in New York.

Anne Burke: Anne Burke, Obstetrics and Gynecology from Johns Hopkins University.

Robert Gut: Good morning. Robert Gut, Vice President, Clinical Development and Medical Affairs at Novo Nordisk.

Julia Johnson: Thank you. For topics such as these being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is in today's meeting to be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their discussion about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics at breaks or lunch. Thank you.

Now I would like to refer to Ms. Kalyani Bhatt to discuss the conflict of interest statement.

Kalyani Bhatt: The Food and Drug Administration is convening today's joint meeting of the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC, Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC, Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of the committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor

children, and for purposes of 18 USC, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today's agenda involves the benefits and risks of drospirenone-containing oral contraceptives in light of the emerging safety concerns that the risk of venous thromboembolism (blood clots that can break lose and move with the circulatory system) associated with the use of these products may be higher compared to oral contraceptives that contain progestin levonorgestrel. Drospirenone-containing oral contraceptives for the primary indication of pregnancy prevention include: Yasmin, Yaz (drospirenone/ethinyl estradiol tablets), Beyaz, Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets), Bayer HealthCare, and the generic equivalents for these products.

This is a particular matters meeting during which specific matters related to drospirenone-containing oral contraceptives will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with the meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the products at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Robert Gut is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Gut's role at this meeting is to represent industry in general and not any particular company. Dr. Gut is employed by Novo Nordisk Incorporated.

With regards to FDA's guest speaker, the agency has determined that the information to be provided by the speaker is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker. Dr. Stephen Sidney has acknowledged that he was the principal investigator of a Food and Drug Administration commissioned study titled "Combined Hormonal Contraceptive Drugs: Thromboembolic Disease and Death Outcomes." The study ended in July 2011. As a guest speaker, Dr. Sidney will not participate in committee deliberations nor will he vote.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

Julia Johnson: Thank you, Ms. Bhatt. Now we will proceed with the FDA opening remarks from Dr. Scott Monroe. Dr. Monroe?

Scott Monroe: Good morning. I hope you can all hear me. I'll introduce myself again. I'm Scott Monro, the Director of the Division of Reproductive and Urologic Products at the FDA. I welcome you to this joint meeting of the advisory committee for Reproductive Health Drugs, and the Drug Safety and Risk Management advisory committee.

The focus of today's meeting is Yasmin, a combination oral contraceptive that contains 3 milligrams of the progestin, drospirenone and 30 micrograms of the estrogen ethinyl estradiol. Yasmin was approved for marketing in the U.S. in 2001 and it was the first oral contraceptive to contain the progestin, drospirenone. Major objectives of today's meeting include the following.

To learn if committee members believe based on available epidemiologic studies that users of Yasmin and other drospirenone-containing oral contraceptives are at an increased risk of thrombotic or thromboembolic events compared to users of oral contraceptives containing other progestins that have been included in the epidemiologic studies.

Another objective is to learn if committee members believe that in the general population of women, the benefits of Yasmin and other drospirenone-containing oral contraceptives for prevention of pregnancy outweigh their risks. If not, are there subpopulations of women for whom the risk benefit profile would be favorable. All combination oral contraceptives pose safety concerns, primarily thrombotic and thromboembolic events, also referred to as VTEs in my introductory remarks.

VTEs, both venous and arterial are observed more commonly in users of oral contraceptives than in non-users. Rates for VTEs in oral contraceptive users, however, are lower than the rates in pregnancy in the post-partum period. The increased cardiovascular risk associated with the use of oral contraceptives was initially attributed to the effect of the estrogenic component. Consequently, the dose of estrogen in oral contraceptives has been reduced several fold since their initial approval in the 1960s.

Beginning in the 1990s with the introduction of several new progestins, attention has also focused on the possible role of the progestin component with respect to the VTE risk of oral contraceptives. At the separate request of the European Regulatory Agency and the FDA, the sponsor conducted two post-approval epidemiologic studies to assess the cardiovascular risk associated with the use of Yasmin. Both of the studies published in 2007 reported no increased risk for VTEs in users of Yasmin compared to users of oral contraceptives with progestins other than drospirenone.

Since 2009, however, several studies, including an FDA funded study, reported an increased TTE risk in users of Yasmin. Virtually all published epidemiologic studies regarding the TTE risk of drospirenone-containing oral contraceptives are based on a comparison of Yasmin to other oral contraceptives and not on a comparison of Yaz which contains a lower dose of ethinyl estradiol and the same dose of drospirenone to these other oral contraceptives. Both the FDA and Bayer HealthCare presentations will analyze the conflicting epidemiologic findings.

As with all epidemiologic studies, methodological issues make interpretation of these conflicting results difficult. Because of these conflicting results, we believe that advisory committee discussion and advice are warranted and will be very helpful to the division in any future regulatory actions regarding Yasmin and other drospirenone-containing oral contraceptives. An overview of the agenda for the remainder of the day is listed on this slide. The FDA presentation in the morning will be split into two parts. After the first part, Dr. Sidney of Kaiser Permanente will present the results of the FDA funded study as they pertain to Yasmin.

Later in the morning, Bayer HealthCare Pharmaceuticals will make its presentation. After lunch, there will be the open public hearing, followed by a brief risk benefit analysis summary by the FDA. The remainder of the meeting will focus on questions from the committee to presenters and committee discussion and voting. I now turn the meeting back to Dr. Johnson.

Julia Johnson: Thank you very much, Dr. Monroe. We'll now proceed with our presentations from the FDA and guest speaker. I would like to remind our public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Gerald Willett: Good morning. My name is Jerry Willett. I'm a medical officer in the Division of Reproductive and Urologic Products at the Food and Drug Administration. My presentation this morning will focus on introductory background information and a regulatory related timeline of key safety events for drospirenone-containing oral contraceptives or COCs.

My presentation will include the following: a brief description of these products, the primary and secondary indications, a timeline of U.S. regulatory actions and pertinent publications that have addressed safety concerns, comments concerning cardiovascular risks for women both in general and those taking COCs, some information on determining efficacy for COCs and lastly, some recent drug utilization information for these products.

Drospirenone-containing oral contraceptives contain a combination of ethinyl estradiol and drospirenone. Ethinyl estradiol is by far most commonly used estrogen in COCs. With its long history of use, the safety of this component of the pill has been very well characterized. Studies have clearly identified a dose relationship for ethinyl estradiol and an increased risk of venous thromboembolic events. Drospirenone is one of the many progestins that have been used in COCs. In distinction to other progestins, drospirenone is a spironolactone analogue.

As such, it exhibits antimineralocorticoid and antiandrogenic activity. Although the antimineralocorticoid activity may result in hyperkalemia, studies have shown that this particular side effect is very rare. This table compares the four drospirenone-containing COCs. These include Yaz, Yasmin, Beyaz, and Safyral. All four products are similar in that they contain 3 milligrams of drospirenone. In terms of the ethinyl estradiol dose, Yasmin and Safyral contain 30 micrograms of ethinyl estradiol, whereas Yaz and Beyaz contain 20 micrograms.

Beyaz and Safyral are the products that contain levomefolate. In terms of the active hormones, Yasmin and Safyral are taken for 21 days, whereas Yaz and Beyaz are taken for 24. Levomefolate in the Beyaz and Safyral products is taken every day. I have bolded Yasmin in this particular table to highlight the fact that most of the safety studies that will be discussed today have evaluated this particular product. The primary indication for all of these products is the prevention of pregnancy.

Yaz and Beyaz have the secondary indications for premenstrual dysphoric disorder and moderate acne. Beyaz and Safyral have the secondary indication of raising folate levels. It should be noted that secondary indications for combination oral contraceptives require that women first choose to use the product for the contraceptive indication. I will cover the event timeline for drospirenone-containing COCs in the next three slides.

The first drospirenone-containing COC to be approved in the U.S. was Yasmin, which occurred in May of 2001. Yaz, the product with 20 micrograms of ethinyl estradiol and the 24 day regimen was approved in March of 2006. Shortly thereafter the secondary indications of premenstrual dysphoric disorder and moderate acne for Yaz were approved.

Two post-marketing safety studies for Yasmin which were required by regulatory authorities in Europe and the U.S. were published in 2007. Both of these studies, the EURAS study and the Ingenix studies, which will be discussed in greater detail by other speakers today, reported no increase in VTE risk compared to other COCs. In 2009, the British Medical Journal published two studies that reported an increased risk of VTE for Yasmin.

The FDA reviewed these studies and in April of 2010 reported the safety findings in product labeling from four publications. These four publications included the two British Medical Journal articles, the EURAS study and the Ingenix study. Later in 2010, the products containing levomefolate, namely Beyaz and Safyral, were approved. In April of 2011, the British Medical Journal published two additional studies that reported an increased VTE risk for Yasmin.

One of these studies was U.S. based and the other was performed in the United Kingdom. The FDA issued a drug safety communication regarding these latest publications the following month. In September of 2011, the preliminary findings from an FDA funded study of commonly prescribed hormonal in the U.S. was announced. The final report was posted online in October of this year and the FDA funded study also reported findings of increased VTE risk for Yasmin.

VTE risk for reproductive age women will be discussed in the following three slides. This will include information on overall risk, risk during pregnancy and the postpartum period and the general risks associated with COC use. Twenty-five years of study data were analyzed by Silverstein and his colleagues for Olmstead County, Minnesota between 1966 through 1990. The VTE rates for all reproductive aged women are presented in this slide. This slide demonstrates the importance of age on the increasing risk for the two principal VTE events, namely that of deep vein thrombosis or DVT, and for pulmonary embolism or PE.

Data from Minnesota over a 20 year timespan evaluated the VTE rates for pregnancy in the postpartum period. As shown in this slide, the VTE risk is by far the greatest in the postpartum period. The total rate for all ages including both pregnancy and postpartum is 20 events per 10,000 person years. This incidence rate is important to consider in light of any studies evaluating VTE risk for women taking COCs, because this rate is usually at least two times greater than that of the risk associated with COC use.

After COCs were introduced in 1960s, safety signals regarding cardiovascular adverse events began to appear. Early studies differ from the more recent studies in that superficial thrombophlebitis was also included in the analysis and the dose of the hormones that were studied in the 60s and the early 70s were much greater than what we see now. To some degree, inclusion of these earlier studies accounts for the relatively wide VTE risk estimate that we see in the literature that ranges from two to ten-fold higher in COC users compared to that in non-users.

An increased risk for myocardial infarction has also been attributed to concurrent COC use. This risk, however, is primarily observed in smokers aged 35 or older and in women with underlying risk factors for coronary artery disease. There have been somewhat mixed results regarding the risk of stroke in women using COCs, especially with more recent studies of lower dose pills. These mixed results have been seen when analyzing both ischemic and hemorrhagic strokes and we also have seen some difference between cohort studies and case controlled studies in this analysis.

Hypertension, smoking, and estrogen dose appear to be some of many important modifying factors in these analyses. When COCs are analyzed for their primary indication of contraception, the Perl Index is one of the primary assessments of efficacy. The Perl Index represents the number of pregnancies that occur per hundred woman years of exposure while the women are taking the contraceptive. Registration trials are usually one year in length. Cycles of use in which backup contraception is used are typically excluded from Perl Index calculations. The lower the Perl Index, the more effective the product is as a contraceptive.

The diagram shown to the right in this slide is found in the U.S. labeling of many of the recently approved COCs. The most effective methods of contraception such as sterilization are shown at the top and then the risk of pregnancy from not using any method at all is shown at the bottom. Then the birth control pills and the patch and the vaginal ring are just in that second box below. The Perl Index in most COC registration trials ranges from about 0.5 to 3 pregnancies per hundred woman years. The Perl indices for Yasmin and Yaz are in the lower end of this range.

This pie chart shows dispensed prescriptions in 2010 for combined or hormonal contraceptives in U.S. outpatient retail setting. The drospirenone-containing COCs Yasmin and Yaz are shown in the upper left with a combined total representing about 16 percent of this market. This translates into approximately seven million prescriptions for Yaz and 5.8 million prescriptions for Yasmin. And with that, I will conclude. The next FDA speaker is Dr. Rita Ouellet-Hellstrom. She'll be providing an overview of Yasmin post-marketing epidemiologic studies.

Rita Ouellet-Hellstrom: Good morning. My name is Rita Ouellet-Hellstrom. I'm the Associate Director for Science within the Division of Epidemiology at the FDA. During this first session and on behalf of the Office of Surveillance and Epidemiology, I will summarize the results of the FDA's passive surveillance system which provides reports from manufacturers, healthcare providers and users. Summarize the results of the Yasmin studies reviewed by the agency to date and provide the rationale why OSE initiated its own epidemiologic study.

As early as 2004, it was noted when reviewing the reports from the FDA's passive surveillance system that differences in risk between the newer hormonal contraceptives at the time, it's been many years since, compared to older products consistently depended on which product was selected as the comparator and how the product was being prescribed. The Yasmin reporting rates for VTE were generally similar, but those for arterial events and death were slightly higher.

At the same time, two post-approval studies had been initiated and results published. I will now briefly summarize the results of these and other studies. Of the two post-approval studies, one was a European and the other included experience of women in the United States. In the European studied, referred to as EURAS, European

prescribers recruited women who received a new prescription for Yasmin or another oral contraceptive. All users who signed the consent form were enrolled.

Personal or mail interviews were conducted at baseline and every six months. In the United States study was completed by the i3 Ingenix investigators. In this study, Yasmin and other oral contraceptive initiators were identified from the United Healthcare database. Yasmin initiators were matched on exposure to two other oral contraceptive initiators using the propensity score. The propensity scores were calculated from clinical information obtained in the six months prior to hormonal contraceptive initiation. Ninety-eight percent of Yasmin initiators were matched. Two percent were not.

Other studies were completed more recently. Two were published in 2009 and one in 2010 and the last two in 2011. Other than the FDA studies published even more recently are not discussed today. I would like to emphasize that the studies discussed today focus on Yasmin and the drospirenone-containing products 30 micrograms of ethinyl estradiol, but not Yaz which contains 20 micrograms of ethinyl estradiol, although Dr. Lidegaard included results for Yaz in his most recent publication. The manufacturer might discuss Yaz in more detail.

Although the cohort studies published incidence information, only the relative risk estimates presented here. Incidence information is available in the background package. Results from the two post approval studies and the Dinger case control study found no elevated VTE risk when Yasmin was contained to a levonorgestrel containing or other oral contraceptive. Both the Lidegaard and the Vlieg studies show the expected increased VTE risk when compared to non-users for Yasmin and LNG.

If we were to compare these products directly it is noteworthy that the ratio of the VTE risk estimates between Yasmin and LNG in all of these studies range from 1.8 to 2.0. The case ctrl study published in 2011 and one U.S. based, the other using the GPRD database, also reported a two to three-fold increase relative risk for VTE. Only two of the eight studies presented so far report on the VTE risk in U.S. women. The FDA study is a third. Many studies compare Yasmin to levonorgestrel containing products, since the LNG products appear to be the preferred contraceptives presented in Europe. However, this is not the case in the U.S.

This is a complicated slide and it presents national dispensed prescription data in the United States between the years 2002 and 2010. Calendar year is noted on the X-axis. The number of prescriptions dispensed in millions are noted on the Y-axis. The number of prescriptions dispensed for Yasmin, shown in the light blue bar graphs, were increasing during the time the studies were being conducted. The subsequent decrease in prescriptions for Yasmin appears to be offset by an increase in prescriptions for Yaz around the year 2007.

Prescriptions for all LNG products, the light blue line, also were decreasing during the time the prescriptions for the drospirenone products were increasing. Although the market presence of the drospirenone products seem to have an impact on the contraceptive market, this slide also shows that the majority of U.S. prescriptions were for the norgestimate product in dark blue at the top, especially on the left side of graph, and other progestin containing products shown by the green line.

So why did OSE initiate another study? There were limitations in the post-approval studies. These studies evaluated one product, which was Yasmin, compared to LNG

product or other oral contraceptives, identified cardiovascular deaths only, and provided limited information of Yasmin's risk in U.S. populations. Unresolved questions included the need to evaluate risk in all newly approved contraceptives at the time, all deaths including sudden deaths, and a more expanded age group which included 10 to 55 years in other U.S. insured groups such as Medicaid, and by product use and prescribing patterns based on suggestions from the passive surveillance system.

The FDA study was initiated in 2008 and the final report is posted on the FDA website. Dr. Stephen Sidney from Kaiser Permanente in Northern California, the principal investigator for this study will now provide an overview of the study design and results. Following Dr. Sidney's presentation, I will provide more detailed discussion and interpretation of the epidemiologic studies noted. Thank you. Now Dr. Sidney will present the FDA results.

Julia Johnson: Thank you. Now we will proceed with the presentation from our guest speaker, Dr. Sidney.

Stephen Sidney: Good morning. Let me begin -- the aim of our study was to assess the risk of cardiovascular disease endpoints for each of three of the newer combined hormonal contraceptives relative to four low dose contraceptives. So this particular report will focus on the risk of cardiovascular disease endpoints associated with Yasmin relative to the four comparators.

Let me first tell you about the study population. We conducted this study at four different sites. Two of them are integrated healthcare delivery systems known in some reports as HMOs. We don’t consider ourself HMOs anymore, just for the general knowledge here. Kaiser Permanente Northern California, Kaiser Permanente Southern California, and two state Medicaid populations -- one in Tennessee that was worked on by Vanderbilt University, one from the State of Washington worked on by the University of Washington.

We used computerized data from each of these sites to obtain enrolment data, demographic information, prescription data, claims data, hospitalization out out-patient visit data, and mortality data were obtained from state mortality files. In all there were over 835,000 women ages 10 to 35 years old who had at least one prescription for one of the seven study contraceptives over the seven-year period from 2001 to 2007 and the use had to be proceeded by at least six months of continuous membership. You can see the size of each of the populations.

You'll see that the Kaiser Permanente populations are larger than the Medicaid populations and when we look at some of these data later, this will be broken out. So roughly about 75% of the population was in Kaiser Permanente and about 25% in the Medicaid population. We did another analysis which will be shown here of over 573,000 women in what we will call the new user analysis. And this is restricted to the very first prescription period for a study contraceptive in women who have at least six months of no use of any contraceptive at all, including non-study contraceptives. So this gives us a group of women starting their first prescription for study contraceptive who have a clean slate prior to that in our study period.

These are the contraceptives we studied. The ones of interest in which we we're interested in examining the risk questions are shown here. Yasmin is the one that we're focusing on today. We will not talk about Ortho Evra or NuvaRing. And the

comparators you see here, there is a range here -- they include a range of ethinyl estradiol doses from 0.18 to 0.35 milligrams.

Our study endpoints were hospitalized arterial, actually thromboembolic events, acute myocardial infarction and ischemic stroke. They were combined because the relative small numbers of the events, we made a combined endpoint here. Venous thromboembolism, which includes hospitalized and outpatient deep venous thrombosis and hospitalized pulmonary embolism. We examined mortality, both total and cardiovascular. We obtained medical records and diagnoses of all the hospitalized cases and these were all adjudicated by physicians. Adjudication of outpatient deep venous thrombosis events were performed only at the Kaiser Permanente Northern California site.

Exposures -- prescription periods included the dates covered by a prescription or a series of prescriptions for a single study contraceptive. We defined an exposure period to each contraceptive as the prescription period plus a 42-day period of what we called indeterminate use, but for the purposes of analyses, the prescription period plus that 42-day period were considered to be current use. The 42 days covers potential, not quite daily use by the woman who's given the prescription. But moreover, it covers the lingering effects of coagulation and perhaps other physiological effects that might impact on cardiovascular risk.

If a second prescription for a contraceptive occurred before the end of the first prescription, we would adjust the start date of the second prescription to the end of a normal cycle of the first prescription, which would generally be 28 days. Follow-up -- follow-up was evaluated independently for each of our outcomes of interest. That is for the acute thromboembolic and venous thromboembolism. End of follow-up was defined as the first of the following events, last date of continuous membership. In other words, once membership ended, we would stop following the individual the 42 days after the date of the end of the prescription use, of all prescription use.

Development of a study endpoint -- the end of the study which was December 31st, 2007. The date of the 56th birthday and the first day of a period of pregnancy. Total person years of follow-up for all use were 898,251. In our new user cohort, the total person years of follow-up were 367,138. Covariates or other factors that we evaluated in the analysis -- we actually looked at 38 different covariates which were known to be involved with cardiovascular risk known to be associated with contraceptive use, and I'll show you just a smidgeon of this on the next slide.

We had some important covariates that could not be evaluated. We did not have data on body mass index. We did not have data on family history of cardiovascular endpoints, in particular, the venous thromboembolism, and we did not have smoking data.

Statistical methods -- we used the COX proportional hazards regressions to estimate the relative risk. The exposure was a four-level variable. We had each of the exposures that we were interested in, as one level. And the comparators, the four comparators were combined together as the other exposure of interest. Age, site, and calendar year of year into the study were included in the models. Established risk factors were included in the acute thromboembolic event models. Other potential covariates were tested individually in the base models.

None of them met our test for inclusion in a final model which would be changing the estimate of relative risk with any of the contraceptives by 10% or more. This is the number of validated study endpoints in our study. I want to just start this by remarking -- for venous thromboembolism we did include non-validated outpatient DVTs or deep venous thrombosis from the three other sites. There were a bit over 200 of those. In our validation that we did at Kaiser Permanente Northern California, we had an 89% validation rate in those.

And I think the other sites might be a little lower, but I think the rates are quite high, because in addition to having to have the outpatient diagnosis of deep venous thrombosis, we also required a prescription for an anticoagulant within 30 days after the date of the event. So they would have warfarin or something else in association with the outpatient of deep venous thrombosis.

So now for the number of endpoints for acute MIs and strokes or ATEs, you can see the numbers here. We have in our Yasmin group, 17 ATEs in all users, 14 in new users. We have quite a significant number of VTEs as you can see here. Total mortality, we had relatively small numbers in the Yasmin group. And cardiovascular mortality, we had very little in our Yasmin group.

This is looking in new users -- the age distribution would be similar in all users, but the age at first study contraceptive use in new users in our Yasmin group on the left and the comparators on the right. You can see the Yasmin users a bit younger in general than the users of comparators. The mean age of Yasmin users was 25.4 years. Mean age of users of comparators was 27.2 years.

I'm not going to focus on this too much. It's a lot of stuff. I wanted to you an example of what we found with our comparators. This is a list of all the covariates which were present in at least 1% of any of contraceptive groups in new users. If they're not on this list, it's that they were less than 1% evident. Most of them are actually lower in the Yasmin group than the comparator group, with the exception of acne, which is somewhat higher in the Yasmin group and I think that's actually it. The others are either just about the same or lower in the Yasmin group.

These are age and site adjusted incidence rates of events. For ATE, you can Yasmin is lower for all users, but somewhat higher for new users. For venous thromboembolism, whether you look at all users or new users, the rates in Yasmin users are quite a bit higher than those for comparators. Total number mortality is somewhat lower for Yasmin users than users of comparators.

These are really our primary findings here. These are really the main findings here. For people who are unfamiliar with these kinds of data for relative risk, let's look venous thromboembolism. You can see that for venous thromboembolism the relative risk associated with Yasmin compared to the comparators was 1.74 and significant: for new users, just about the same, 1.77. This means the risk of getting a venous thromboembolism is 177% or 77% higher with Yasmin use in new users than in users of comparators.

And there's another notable finding here. For acute thromboembolic events in new users, there was about a doubling of risk with Yasmin, but that was not evident in the all use group. Total mortality, there was no significant difference from there being no risk at all. This slide compares the risk by duration of use in new users in Yasmin relative to comparators. We'd expect to find it higher because that's typical and it is

higher in the early time after the use. In the first three months it's about twice as high in Yasmin users relative to comparators.

Now, what bothers a lot of people, every person I've shown this to, is what's going on six to 12 months out. And for this, you have to take a look at the next slide here, which shows the actual incidence rates by time period in Yasmin users and comparators. And if you look at that seven to 12 month period, it's actually six to 12 months, you can see that for Yasmin, the risk is highest in the first three months; goes down in four to six months; goes up minimally or slightly, six to 12 months; and then it goes down after that.

What happens with the comparators is that there's really kind of an abhorrently low level at six to 12 months. So that when you make the comparison at that particular time period between Yasmin and the comparators, you see that apparent abhorrency (sic) in the relative risk. Now these were prespecified intervals. Now if, for example, we had chosen three to 12 months instead, you wouldn't have seen anything. It would have just looked like a dip. But I think it's important to understand the difference between the relative risk during that time period and the actual incidence rates. The highest risk with Yasmin is indeed during the first three months after use.

We then took a look between the Kaiser sites; did the same analysis in Kaiser Permanente sites and the Medicaid sites. Remember Kaiser Permanente is about three-quarters of the population. We see for acute thromboembolic events, that finding for new use is evident only in the Kaiser Permanente Group. However, all the findings for venous thromboembolism are similar between the two sites. And they're a little bit lower at the Medicaid sites. They're not statistically significant at the Medicaid sites, but again you have to remember they have much fewer data. There is only 25% of the population is at the Medicaid sites.

And the -- I think this is the final finding slide here. We then looked at it by stratifying the groups by age, looking at the younger part, under 35 years of age, compared to the older part of cohort. In this instance, we see that the findings for venous thromboembolism are seen predominantly in the younger group. Much stronger effect and also significant in both the all user and the new user group, about twice the risk. And then we have this interesting finding for acute thromboembolic events in new users in the older part of the cohort only, with a 2.6 relative risk.

Strengths of the study include a large diverse exposure cohort study. We were able to validate most of the electronically identified study endpoints, all of the hospitalization and outpatient DVTs from one of the sites. And we had a new user analysis that required no use of any contraceptive at all for at least six months prior to the date of new use. Limitations included reliance on electronic pharmacy data to ascertain CHC exposures as well as covariates. The absence of data on key covariates I've stated before -- BMI, smoking, and family history, validation at outpatient DVTs only at one site, and the absence of longer term prior use data beyond six months.

In summary, new use and all use of Yasmin were associated with increased risk of venous thromboembolism relative to low dose estrogen comparators. And new use of Yasmin was associated with increased risk of -- I'm sorry, that should be acute thromboembolic events, not just AMI, in older women, but all use was not. This particular relationship with acute thromboembolic events, these are inconsistent and may be worthy of further study. Thank you.

Julia Johnson: We now will proceed with our last FDA presentation. Following that, I'm preparing the committee to consider questions for the FDA. Dr. Ouellet-Hellstrom?

Rita Ouellet-Hellstrom: Again, good morning. I will now present supporting documentation for our preliminary assessments of the Yasmin studies reviewed by the agency. Some of these studies report no relative increased VTE risk, whereas others do when comparing Yasmin to older contraceptives. I will explore with you the main reasons why I believe the studies present different results. Only the more salient points will be discussed, since 20 minutes is just not enough time to address all the work done by the investigators and all the issues raised by these studies.

Because this is a complex issue, we will summarize our preliminary assessment first. Yasmin appears to be associated with a consistently higher relative risk when compared to other combined hormonal contraceptives in the more recent studies, particularly among younger Yasmin users. However, in the next few minutes, I will present supporting documentation that show Yasmin users may be different from users of comparator products. Dr. Sidney already addressed some of that.

I will also highlight differences in exposure definitions. Important confounders such as BMI, personal and family history of VTE, lifetime use of hormonal contraceptives are not recorded in claims databases, although proxies have frequently been used. Finally, I will present information that suggests that channeling may be an important factor in explaining differences seen here. I believe the contributions of these factors need be evaluated before concluding that Yasmin carries a higher VTE risk than its comparators.

During this presentation, I will provide examples from the studies that best illustrate the concept I am trying to show. This, in no way, should be interpreted as an endorsement of which study I deem more reliable. All the studies have strengths and limitations and I believe we can learn from each if we keep an open mind. I will present differences in study populations, then highlight differences in exposure and outcome definitions while also addressing confounding.

Finally, I will present evidence for possible channeling or prescribing differences. My presentation will summarize FDA's preliminary assessment of these issues, and I ask for your consideration during the discussion period. I would like to emphasize that all the topics discussed are interrelated. So it was very difficult to select examples to illustrate one discussion point while ignoring the others.

Are Yasmin users and those from comparative populations similar? I will age as an example to illustrate. We note in this slide that the mean or average age of the study populations is similar across the cohort studies and is higher in the case control studies. This is not surprising. But what I would also like to point out and will illustrate in the next slides is that the slight differences in mean age may represent differences in age distributions of the study populations. Because the FDA study adjusted for age only in the analysis and included different datasets, it was possible to examine age differences by databases.

In addition, FDA has access to nationally projected drug use information which contains some demographic information. This slide compares the age distribution of the users in the Kaiser, the Medicaid, and the IMS databases; the latter representing nationally projected information of users in the United States. Examining this information we note that Yasmin users are generally younger than levonorgestrel users

in all datasets, but especially in Medicaid. I'd like to note that the LNG group here contains the levonorgestrel product that has 30 micrograms of ethinyl estradiol only.

The age distribution of Yasmin in Kaiser is more closely aligned to the age distribution of Yasmin users in the national dataset. But the age distribution in the Kaiser and the IMS databases is different for LNG users. We see fewer prescriptions for Yasmin with increasing age in the all populations with the exception of the LNG where we see increasing prescriptions with age only in the nationally representative population. Is this evidence for channeling or prescriber preferences?

Two studies illustrated here have shown an interaction with age. Although the absolute risk of VTE increases with age, the relative risk for VTE is highest for younger Yasmin users. Two other studies by Jick and Lidegaard also noted an increased use of Yasmin in younger users, especially new users. Why do younger women have a higher relative risk for VTE?

On the other hand, older women who are new users may have a higher risk of VTE, although most studies evaluating ATE risk, lack the data and the power to shed more long-term on this issue. In the EURAS study, the incidence of VTE is similar to Yasmin users and users of the other comparators. In the FDA study, the incidence of VTE is lower in the comparator groups. However, in both studies the incidence of ATE and mortality appear to be higher in the comparator groups than in the Yasmin groups. Are these differences in incidence rates reflective of a truly lower ATE risk for Yasmin or are they reflective of some other dynamic at work in these populations?

In the next slides, I will present trends in data prescription over the study time period. This slide shows a proportion of prescription trends over time in the United States using IMS Vendor One (ph) database, which represents nationally projected drug use information. We see that during the FDA study time period, the proportion of prescriptions for Yasmin, noted as DRSB_30 in this slide, were increasing after market introduction practically throughout the study period. We note a decline in the proportion of Yasmin prescriptions beginning in 2008, concurrently with an increase in Yaz prescriptions.

The proportion of prescriptions for the LNG product, again the 30 micrograms ethinyl estradiol product, which in this slide did not change much over the study time period suggesting possibly selective use or prescribing. It is likely that these changes and trends over time could indicate changes in provider or consumer preferences. Unfortunately, the available information reflects only U.S. trends and may not address differences seen in the European studies.

Exposure definitions also varied across studies. Some studies included all women who received a new prescription, the EURAS and all users and the FDA study. Other studies were more restrictive and evaluated risk in new users only. But the definition of new use also varied by studies. Many studies define new use as having no documentation of a study contraceptive in the prior prespecified period. Other studies required evidence of no prescriptions of any hormonal contraceptive whatsoever in the prespecified period. The prespecified look back period also varied by study and it has ranged from four to six months. Do these differences translate into different relative risks? Maybe.

When comparing risk estimates within studies, the relative risk for VTE does not appear very much by exposure definition in the FDA study. There is more variation in

the Lidegaard analyses. The greater differences however are seen when comparing risk across studies. Differences in exposure definitions may be more significant when comparing ATE risk as seen in the FDA study. Since no other study presents this information, this result will need to be confirmed.

Now I would like to address confounding and differences in how these studies adjust for this. All studies adjusted or matched for age and calendar time. Some studies adjusted for or examined duration of current use as well. But the expected known important confounders such as BMI, family and personal history of VTE, smoking and lifetime history of contraceptive use cannot be obtained from claims data or even from medical records. Some studies have used proxy information from the dataset such as obesity and education.

Only three studies captured this information which was attained directly from interviewing users. Two of these studies showed no increased risk in VTE and one did. One of the post-approval study matched Yasmin initiators to initiators of other contraceptive products using a propensity score. A score that summarizes or weighs each users probability of being prescribed Yasmin, whether or not Yasmin was prescribed. This score was calculated based on as determined by the investigators, expected or known information from the claims databases in the prior six months, and included more comprehensive information on laboratory tests and procedures, clinical diagnoses, and other medications used.

Although some of this information may have been captured by other investigators, Dr. Sidney and Dr. Jick, those investigators applied the 10% rule which means that each variable would be included in the analysis if it changed the risk estimate by 10% or more. In those studies, none of the variables evaluated produced this 10% change, therefore none were included in the analytical model based on this rule.

When both adjusted and unadjusted risk estimates are provided as seen on this slide, adjusted estimates are either lower or similar to the unadjusted rates for VTE when using the same comparator in the same population. Covariates used for adjustment within a study appear not to change the risk estimates significantly when comparing contraceptive products. Greater differences in risk estimates, however, are seen across studies.

Does VTE risk change with tighter control? Maybe. Although at first glance, this slide may suggest that better adjustment leads to lower VTE relative risk estimates, we must keep in mind the population and comparator differences already presented that may play a role when comparing risk across studies. In addition, adjustment variables presented here are for known or suspected confounders. Are there other confounders we do not know much about?

In the following slides, I would like to present evidence to show that channeling may be an important factor for Yasmin users. All contraceptive products are effective at providing contraception. So which product is prescribed may depend more on other health conditions present. The literature on prescribing patterns is overwhelming European and may not reflect U.S. prescribing patterns. Nonetheless, examining information from the studies and FDA's drug use data, we know possible directed prescribing.

Use of Yasmin is associated with women who also have codes for menstrual cycle problems and polycystic ovary syndrome with its associated symptoms, acne, hirsutism

and alopecia. Adjusting for some gynecological disorders, for example, menstrual cycle disorders and inflammation of the pelvic area also appears to lower VTE risk in studies for other contraceptives. Are these comorbid conditions important? Are these women at increased risk for VTE? Information from the literature is sparse and the VTE risk needs to be evaluated for these conditions.

In the next few slides, I will provide examples showing that use of Yasmin is associated with women who have codes for these health conditions. Drospirenone is reported to improve acne and hirsutism. Spironolactone is a product sometimes used for treating acne and PCOS and hormonal contraception is recommended while on spironolactone treatment. In the FDA study, acne was present twice as frequently among Yasmin users, especially younger users, than the comparator (COMP), despite the fact the COMP also included the norgestimate containing contraceptive long approved for acne with contraception.

There is no reason to believe, based on the scanned literature, that acne by itself places a woman at a greater risk for VTE. Acne, however, is thought to be present in about 10 to 34% of women with polycystic ovary syndrome and is one of the symptoms in addition to hirsutism and alopecia frequently associated with PCOS. PCOS women tend to be overweight and possibly at increased risk of experiencing a VTE when compared with women without.

A study by Schwan (ph) and Chung referenced in the background package, showed a nearly two-fold increased relative VTE risk, although this risk estimate included women on a hormonal contraceptive. When examining the Wolters Kluwer's health current product analyzer data we note codes for acne, hirsutism, and premenstrual tension are associated with all study contraceptives between 2007 and 2010 in women younger than 26 years of age. The codes were present twice as frequently with the drospirenone products compared to the levonorgestrel products.

The proportion of codes associated with a norgestimate product which also has an approved indication for acne and contraception for many years, it's 30 to 50% lower than for the drospirenone products. The same trends are seen for women in all age groups, but the proportion of patients with associated codes decreased with age for all contraceptives. And you can find this information in the background package.

According to the SDI Physician, Drug, and Diagnosis audit, dysmenorrhea codes are present as frequently with all study contraceptives. Acne is associated with both products that have an approved co-indication, but only Yasmin is associated with PCOS and although not presented, this was true at all age groups. More information again is available in the background package.

Although all studies show an absolute increased VTE risk with age for all products, Yasmin appears to be associated with consistently higher relative risk when compared to other combined hormonal contraceptives in the recent studies. Although of concern is the increased relative VTE risk observed for younger women and that younger women are likely to have other comorbid conditions.

I have presented supporting documentation that show users may be different from users of other comparative products. I've also highlighted differences in exposure definitions and the difficulties in identifying confounders and adjusting for them across studies. Most, but not all studies that adjust for important confounders such as BMI, personal and family history of VTE, lifetime use of hormonal contraceptives do not show an

increased relative risk of VTE, but these may not be the only confounders contributing to differences in risk.

Finally, channeling or differences in prescribing patterns may play an important role for Yasmin. We believe the contributions of these factors need to be evaluated and confirmed before concluding that Yasmin carries a higher VTE risk than its comparators. The investigators of these studies have done a lot of work, only some of which could be highlighted today. Although we have made a preliminary assessment of the information, we ask for your thoughts and considerations in assisting the FDA with its interpretation of the study results. Thank you.

Julia Johnson: I would like to start off by thanking all the FDA speakers and our guest speaker for their presentations. We now have time for clarifying questions from the committee for the FDA and the guest speaker. I would ask the committee members if you have a question to raise your hand. Ms. Bhatt will record people's interest in asking questions and just to remind you that we have about 20 minutes to ask questions. If we do not get to all of the questions this morning, there will be additional time in the afternoon for those questions to be presented to all of the speakers. So if you would kindly raise your hand with questions. Yes, Dr. Almazor?

Maria Suarez-Almazor: Yes, I'd like to expand a little bit more on the role of smoking as a confounder. From the data that was presented, Yasmin was used mostly by younger women who are more likely to smoke and that was not adjusted for in Dr. Sidney's study. So I was specifically interested in knowing whether the studies that adjusted for smoking had a lower risk than those that didn't.

Julia Johnson: So who would like to answer that question?

Rita-Ouellet-Hellstrom: Not too many studies adjusted for smoking, unless it was recorded in the database, unless the EURAS study did, and it's not clear when reading both their study result report as well as the published report, what exactly was included as an adjustment and what contribution each of these variables contributed to the adjustment.

Maria Suarez-Almazor: And is there any evidence and maybe this is a question for Dr. Sidney, that for the age groups that were included in the study, there is a difference in the smoking rates.

Rita-Ouellet-Hellstrom: Certainly, Dr. Sidney could address that.

Maria Suarez-Almazor: The Medicaid and the Kaiser Permanente populations.

Stephen Sidney: Yes, I will respond to that by saying that we don't have the data to really answer that in those populations.

Julia Johnson: Thank you. Now, Dr. Hillard?

Paula Hillard: So I'd like to ask the FDA, the issue of channeling has been addressed and the implication is that the question about whether there would be channeling toward the use of Yasmin for individuals with PCOS, acne, and obesity, and I'm wondering if they can address the question as to whether there is any evidence for channeling away from levonorgestrel containing pills because they are perceived as being more androgenic, and so individuals with PCOS, acne, and hirsutism might be less likely to be prescribed those medications containing levonorgestrel?

Rita-Ouellet-Hellstrom: That's certainly the case and when I presented the incidence information for LNG and ATE and mortality, there's I believe, a suggestion that there is channeling to and away from products. But we don't have any evidence specifically to validate that and I believe that that work needs to be done and we hope that all the clinical individual members of this committee can help us with that.

Julia Johnson: Dr. Hernandez-Diaz?

Sonia Hernandez-Diaz: I have questions for Dr. Sidney. If we focus on the new user cohort, can you tell us more about the average follow-up since initiation of oral contraceptives, how many months of follow-up in databases were available for the patients and if there was any difference in the risk ratio, the hazard ratio over time?

Stephen Sidney: I don't have the numbers on the top of my head. Okay. Thank you. If you don't mind, I can look them up here. Are you interested in new user, all user, or both?

Sonia Hernandez-Diaz: We can focus on new users.

Stephen Sidney: New users, yeah. So we have an average of -- for drospirenone the average number of days of use is 268. So about nine months. For the comparators it is 236, so it's somewhat less.

Sonia Hernandez-Diaz: And did you plot any survival curve or did you see any difference in the hazard ratios over time?

Stephen Sidney: We didn't do that, but we have -- we're using a COX proportional hazard, so it's going to -- it should take care of that pretty well. We didn't actually do surgical curves.

Sonia Hernandez-Diaz: Okay. Can I ask more questions?

Julia Johnson: Yes, one more.

Sonia Hernandez-Diaz: In the valuation study, were the adjudicators to the --

Stephen Sidney: Yes, adjudicators were blinded.

Sonia Hernandez-Diaz: So I don't know if you look at this, but did you find any difference in the proportion of adjudicated cases between the exposed groups in the references?

Stephen Sidney: Between the exposed and --

Sonia Hernandez-Diaz: Yasmin and the comparison. So more cases validated or confirmed in one group or the other.

Stephen Sidney: I actually could not answer that. I don't think we -- we did not look at that. We, basically, tried to get all records on all the hospitalizations , but I can't answer it by preparation.

Sonia Hernandez-Diaz: I have one more question, but I can wait.

Julia Johnson: We'll go through the list and come back to you. Thank you. Dr. Orza?

Michele Orza: I have the same problem. I have five questions, but I think they all have short answers. How sure -- okay, three. The three shortest ones. I guess this is for the FDA folks. How confident are we that we don't have a publication bias problem here? That we've really seen all of the studies and all of the data that's out there? Secondly, beginning with Olmstead study, which is what we're kind of using as our baseline, do we have for any these studies or hopefully all of them, any breakdowns by racial and ethnic groups to know whether there are any differences there? And I guess, the third would be, I guess for Dr. Sidney. I find it hard to believe that Kaiser doesn't have data on BMI and smoking, especially for women to whom they're prescribing birth control pills. Are you able to look at subset or would you at least have that data?

Stephen Sidney: We would be able to do that. We haven't done that. The reason has to do with our own data sources. We started collecting those things in the early -- electronically in a way that they would be accessible in the early 2000s. And it's not until well over halfway into this study that it might even be somewhat systematic, but even there you're going to be missing a quite a bit of it. If you started the study last year or two, you'd probably have it on most people.

Julia Johnson: So the answer is to Dr. Orza's first questions? Dr. Ouellet-Hellstrom?

Rita-Ouellet-Hellstrom: Do you want to address the Olmstead?

Julia Johnson: If you could go to the microphone, sir.

Stephen Sidney: I mean obviously that's a select population in Minnesota. I don't have the data from the Kaiser or the FDA's funded study though.

Rita-Ouellet-Hellstrom: I will try to address the question on whether we have publication bias. That may be the case if we don't know that a study has been done. But we do have -- received from the sponsor, lots and lots and lots of reports, interim reports, and we have the published Yasmin products. Now there are some studies going on. Probably the sponsor will address that later today on other drospirenone studies that are ongoing, but we only address the studies that were published and completed to date and those refer to Yasmin.

Julia Johnson: Thank you. Dr. Winterstein?

Almut Winterstein: I've two questions, short ones. The first, on polycystic ovary syndrome, in the FDA study in the background material that was provided to us, I saw a 0%. Did I see that correctly for each exposure group?

Rita-Ouellet-Hellstrom: Could you repeat that question? I'm not sure --

Almut Winterstein: The polycystic ovary syndrome as a risk factor that you mentioned, Dr. Hellstrom, in the background material that was provided to us, your assessment of the FDA study, I think I saw somewhere a table that said that there was a 0% rate which surprised me a little bit. Could you comment on that?

Rita-Ouellet-Hellstrom: Dr. Sidney will address that.

Stephen Sidney: It is not 0%. It's low, less than 1%. There are PCO cases.

Almut Winterstein: Is that consistent with the literature? I would have expected that there is a larger prevalence than that.

Stephen Sidney: That might not be the entire prevalence. It's the percentage in which there was a diagnosis within six months prior to the use, where we could find the diagnosis. And of course, there's under diagnosis of that condition as well.

Almut Winterstein: So whether this was an indication or not, we really may not totally know whether Yasmin users --

Stephen Sidney: The prevalence was, I mean it was very low as ascertained that way, but it was not zero.

Almut Winterstein: Then as a follow-up to this, I mean my arms around channeling and looking at the -- and I've read so many studies that I even don't know where I saw this, but there was actually one propensity score comparison of Yasmin users versus the comparison group and the propensity scores looked extremely well aligned and looking at any kind of comparison of covariates as they have been presented by the various studies, they look pretty fairly aligned. So while I understand that there might be a concern for channeling, I don't see it.

And then looking at the -- polycystic ovary syndrome has really a very low prevalence. If acne is -- there's 2% difference between the two groups. I'm still not getting at how a hazard ratio of 1.5 can drop to 1.0. So I you could comment a little bit more on your concern about channeling and to what extent you really think that could produce a very significant risk -- not a very, but a significant risk to no risk, and whether you see that really could explain the whole story here.

Rita-Ouellet-Hellstrom: The concern that we have is -- first of all the rates in this population of women is very low. So a few cases aggregating in a particular area may influence the risk estimate, but we do see that -- we were looking at possible differences in populations and these are the confounders that we potentially could be a problem. But we're limited with the evidence in the reports that we have. My concern is using PCOS and acne as examples. I wanted to express that are there other confounders that exist that we don't know about. And the concern that I have is that the risk estimates seem to be very, very similar, between 1.5 and 2.0 expect for the Parkin study which is at 3.0.

And no matter how we adjust it, the risk estimate still hovers around that. And so, what is happening? It was an attempt to try to tease that out. And the FDA study was initially initiated to first of all assess whether there was a risk, as if there's no risk, then we can't do any further work. But we initiated it with the thought that maybe it would be an opportunity to explore the population as well as prescribe characteristics that could shed some light on it. Now it could be that Yasmin has the higher risk. We don't know for sure, and we presented the evidence that we have, or our thinking so far.

Julia Johnson: Thank you. Now, Dr. Kittelson?

John Kittelson: Yes. A point of clarification. There seems to be age interaction that's coming to light here. One is that of interest, but the second part as long as we're multiple part questions, is on the -- adjusting for confounding ages, I think just a factor stuck in the model, is that now averaging over those interactions?

Stephen Sidney: I'm not sure I've got the point of question (inaudible).

John Kittelson: Well so the risk differs by different age groups.

Stephen Sidney: Yes.

John Kittelson: But if you just put in age into a proportional hazards model as an adjuster, you're now going to average over those.

Stephen Sidney: That is correct.

John Kittelson: You're not going to split those out.

Stephen Sidney: That's right.

John Kittelson: Otherwise, you'd have to be presenting -- adjustments in each age group.

Stephen Sidney: That's correct.

John Kittelson: Okay. Thank you.

Julia Johnson: Dr. Stovall?

Dale Stovall: Thank you. I had two questions. I guess in the Kaiser database, number one, you talked about adjudication of outcomes of VTEs et cetera, but I didn't hear a lot about exactly what the criteria were. Were those venograms, Doppler studies, what was actually used? Secondly, commonly when patients do have VTEs in the hospitalized setting or outpatient, they're tested for thrombophilias. And do you have any data in regards to factor V Leiden mutations, protein C, protein S deficiency antithrombin? And I guess the comment I had, would it be nice to see not only relative risk, but absolute risk changes as well.

Stephen Sidney: Okay. So let me make sure I have the questions one by one. The adjudication criteria, generally they're in our report generally -- I mean to be verified, they would require an imaging study which would -- you know, generally for DVT via a Doppler, there are a variety of other techniques that are included in that. For pulmonary embolus, it would generally be a scan. But we have a variety of imaging modalities involved in that.

Second part of the question again, oh so about the various inherited thrombophilias. No, we don't specifically -- I'd have to go back, but we do have some -- there is some code that captures the basically coagulopathies that we looked at was very low and didn't contribute to our risk. But we really don't have -- in that number of events, there's clearly going to be some of those going on and we don't have that information.

Julia Johnson: Dr. Gilliam?

Melissa Gilliam: This is for I think both the FDA and Dr. Sidney. I'm interested in the definition of non-users, and it seems that this is six months of non-use for a selected period of non-use. Are there any analyses that look at naïve users? So people who have never used a hormonal contraception, and specifically if there's a difference in age, might we be comparing hormonally naïve people to people who have used hormones in the past?

Stephen Sidney: I'll first answer from our study. No, I mean that's obviously the big question. It's one of the big questions. And we could have the potential to look somewhat further back in

our data, but you're limited by membership. The only way to get that kind of history is to do an interview I think.

Julia Johnson: Yes, Dr. Tepper?

Naomi Tepper: Hi. Yeah, actually that was sort of my question as well that Dr. Gilliam just asked, whether it's possible, if someone could clarify if any of the studies looked at whether there were women who previously used OCs longer than six months ago. Is it possible that women were weeded out who maybe used OCs remotely in the past, and either developed a VTE or had a risk factor, and is it possible that that could impact the results?

Rita-Ouellet-Hellstrom: I will attempt to answer that. Yes, to your answer. It's possible. With claims databases, there's a look back period and it can be six months, four months, 365 days. The longer look back period you include the fewer people you get in your studies. I would say that in order to tease out that concern of yours, and it is also a concern of mine, is to look at young women, less than 25 years of age. And in the FDA study, if you see in the background package for the incidence rates between all users and new users, there's not that much difference.

You see a bigger difference as the women get older. And apparently the incidence for VTE is higher in "new older users." The Seeger study, the i3 Ingenix also did split out their analysis by looking at all users and then initiators as best they could in their study. But the numbers then become very, very small and it's impossible to really know what's going on. I think the only studies that could address that would be the EURAS and those that had patient interview, but that information is not clear on the reports or publications.

Julia Johnson: Dr. Montgomery Rice?

Valerie Montgomery Rice: I'll make my comment a question so I can be attentive to the rules. This is to the FDA. If the FDA study was requested because of all of the previous data and to give some clarification. I am challenged by the fact that we would not have looked at smoking or BMI or racial or ethnic differences because we definitely looked at computerized databases and looked at demographics. So did we request that and it was just not available in the record? Or did we not believe at the time that smoking was a risk factor for women taking oral contraceptives for VTE?

Rita-Ouellet-Hellstrom: Well, one of the reasons we selected Kaiser is we were hoping that that information would become available. But if you go back to the communication that we made, first of all we wanted to assess if there's any risk, and then we were planning if there were risks to evaluate the reasons why. And then we would consider going for a personal physician or interviews, but we haven't gotten there yet, but the intent was to get it eventually.

Valerie Montgomery Rice: Because when we outlined the study though, we -- I'm sure we put -- we gave them some parameters of confounders to -- for data that we would capture. Isn't that correct?

Rita-Ouellet-Hellstrom: Well we knew they wouldn't have it for the initial phase of the study.

Valerie Montgomery Rice: We knew they wouldn't have smoking information and racial ethnic information?

Rita-Ouellet-Hellstrom: Well, racial, yeah. Well Kaiser, Dr. Sidney can address that. Kaiser is overwhelmingly white women.

Unidentified Participant: But I think to clarify, the study was designed in two phases. The first phase was to look at the electronic data and that's what you heard presented today. That's been completed. The second phase of the study was previously proposed, but has not yet been funded to proceed and then get additional information that's not available electronically which is a lot of confounders that we know we want to look at.

Valerie Montgomery Rice: So let's make sure we understand. So smoking was not captured in their electronic data, as well as weight and height, that you can calculate a BMI. That is not captured in Kaiser's electronic database.

Unidentified Participant: Not at the time that we initiated the study which was in 2008, but I'll let Dr. Sidney update us on that.

Stephen Sidney: Yeah, let me clarify a couple of these points. I think I've explained, answered the question about smoking a little bit earlier. The question about race, ethnicity has evolved and we do have at this point and it's been kind of a moving -- there's a long history to it. Long and short of it is that we have some reported race, ethnicity now on about 65% of our population.

We have an algorithm that's been developed by Rand (ph) that's been adapted from our use that will purportedly if you take a person's surname and where they live, it'll give you probability, probabilistic distribution, but that doesn't work really well on an individual level. So that's where it is. Actually, Kaiser Permanente's making a big national initiative and we've trying to improve that, but for the purpose of this study, it doesn't really help out. So it's being systematically collected now.

Valerie Montgomery Rice: And we saw the same challenge with the Medicaid database. Is that correct? Okay. So I have one other quick question.

Stephen Sidney: There's one other thing I wanted to say, and just wanted to -- Rita had said that the Kaiser Permanente is overwhelmingly white. That is not the case. It's about 70% white.

Julia Johnson: Just before your next question, I just wanted to tell the -- ask the committee for their indulgence in allowing us to go past our time for break and to allow just five minutes for a break at five minutes of 10:00. If that's acceptable, we'll proceed. Dr. Montgomery Rice?

Valerie Montgomery Rice: Dr. Sidney, the question is to you then. So when I look at -- when you looked at the information stratified by site, and the VTE for Medicaid population which you said accounted for only 25% of the study, there was no statistical difference in the VTE rate compared to your Kaiser site. What do you --

Stephen Sidney: No, I didn't say that exactly. I said that they were in the same direction. There was a similarity particularly with I think it was the VTE. I don't have the numbers in front of me. There actually was a site interaction, there was a statistical interaction between the site. A statistical --

Valerie Montgomery Rice: So you don't perceive any difference in those populations that you can account for?

Stephen Sidney: I don't perceive -- wait a minute, let's --

Valerie Montgomery Rice: Or were there any differences other than the Medicaid population? Was there younger population of women --

Stephen Sidney: Oh no, there's huge differences between the population. Not that they're younger and you and I know that.

Valerie Montgomery Rice: No, no, no. I'm talking about from what you presented; the data that you presented.

Stephen Sidney: In terms of the rates? Are you speaking about the rates themselves?

Valerie Montgomery Rice: The rate?

Stephen Sidney: Yeah.

Valerie Montgomery Rice: Yes.

Stephen Sidney: Okay. They're higher in the Kaiser Permanente population. They're somewhat lower, they're in the same direction and I think if you look them, they're not a not huge amount different for those particular ones that I said they weren't a huge amount different. The ones in the Medicaid sites are not statistically significant. That's a smaller group.

Valerie Montgomery Rice: That's what I was asking. I wanted to make sure I understood that based on the data that was presented.

Stephen Sidney: Right.

Julia Johnson: Thank you. And I'd like to make a correction that actually we go through until 10:00 for our break. If we need that time, we would again ask that we just have a five minute break from 10:10, but we'll see how things go. Dr. Kaboli?

Peter Kaboli: Yes, I have a question and follow-up to Dr. Kittelson's about age. So it's my understanding that age, that the Yasmin users are younger in general, younger users, correct?

Stephen Sidney: That's correct.

Peter Kaboli: Okay. And it's also true that VTE risk goes up with age, right?

Stephen Sidney: With age, yes, that's correct.

Peter Kaboli: So wouldn't -- in spite of the adjustments that were used and the methods used, wouldn't that lower age still bias towards the null? That there would be no difference in rates of VTE? So if there's going to be -- this gets to this bias, right?

Stephen Sidney: Okay.

Peter Kaboli: So if there's some bias because of age, wouldn't it bias towards the null, showing that there's no difference, and therefore the rates that we're seeing may actually --

Stephen Sidney: I'm not sure why there's this question about if there's bias. I'm not sure what bias you're talking about.

Peter Kaboli: About age. Age, itself.

Stephen Sidney: Age itself biases? I'm not sure what you're meaning in terms of age -- something that biases --

Peter Kaboli: So if the rate is higher in Yasmin users, right? I'm sorry. The age is younger in Yasmin users.

Stephen Sidney: Right.

Peter Kaboli: In general.

Stephen Sidney: Uh-hm.

Peter Kaboli: Yet risk of VTE goes up over time with age, wouldn't that in spite of the adjustment, bias towards the null in showing and association between the two?

Stephen Sidney: Between?

Peter Kaboli: Between exposure and the event? VTE?

Stephen Sidney: Oh, I see what you're saying. Yes, it could. I mean I see what you're saying. Yeah, there would be some potential for that.

Peter Kaboli: Okay.

Rita-Ouellet-Hellstrom: I'd like to add though that for the FDA study in especially using the COX proportional hazard model, they adjusted by five year age groups and within the five year age groups, they adjusted for individual age. So there's a double adjustment there.

Julia Johnson: And I'd like to thank the committee for their patience. Now, Dr. Wild?

Bob Wild: Yes, I have several questions. One, for the Kaiser study, is their formulary fixed in any way based on cost? In other words, is a physician easily able to make a judgment for what pill to use by his clinical acumen or is there anything related to cost restrictions within any of the databases?

Stephen Sidney: I can't speak for Medicaid. For Kaiser Permanente there's a variety of formulary contraceptives. I've spoken with the chief and the leader in Northern California of the OB/GYN group. So what I can say is this. That's there is no particular guidance given to any physician about what to use.

Bob Wild: But is there a limited formulary that Kaiser employs because of cost?

Stephen Sidney: Yes, there is.

Bob Wild: So a person would more likely to prescribe based on cost than clinical indication? Yes or no, or can you determine that?

Stephen Sidney: By and large, the Kaiser Permanente physician will prescribe from the formulary.

Bob Wild: Formulary, I mean is there cost preference? Do they have to go out of the system to use something niche?

Stephen Sidney: No. There's a Kaiser Permanente -- most patients will use a Kaiser Permanente pharmacy in most -- which uses contraceptives that are within the Kaiser Permanente formulary.

Bob Wild: And that's a broad range of all the prescription we're talking about here?

Stephen Sidney: Yes.

Bob Wild: Okay. The second question I have is on adjudication. Were these centrally adjudicated or locally adjudicated?

Stephen Sidney: Centrally.

Bob Wild: Centrally. And you said there was for one subset, 200 were adjudicated with an 89% you thought.

Stephen Sidney: These were the outpatient DVTs.

Bob Wild: Okay. Was there a sensitivity analysis done on the estimates assuming the lack of adjudication or misclassification and did that affect the result?

Stephen Sidney: You mean for the ones that weren't adjudicated?

Bob Wild: Or even for those that were not adjudicated correctly. Was there an adjustment in the risk estimate?

Stephen Sidney: No.

Bob Wild: Okay, and the third question --

Stephen Sidney: I will say this though. There was a separate analysis, I think it's the main report on hospitalized VTEs only, which were all adjudicated and that was consistent, I think a little bit higher than the overall relative risk for VTEs.

Bob Wild: And for the FDA group, I think you may have -- you may give us some insight about this, but do we have information on demographics, physical activity, inactivity, occupation, all the other potential confounders that may be related to thrombotic risk?

Rita-Ouellet-Hellstrom: No. All of the claims databases do not have that information.

Bob Wild: So in the next planned study, does that include some of that?

Rita-Ouellet-Hellstrom: I we were to go and get patient interviews, yes, and other things, but it does not apply to today, so I will not mention it.

Julia Johnson: Thank you. Dr. Schisterman?

Enrique Schisterman: Yes. Clearly this took a lot of work and I wonder from the work that is not presented, is some sensitivity analysis on unmeasured confounders given that it seems that there is

a sense that unmeasured confounders as a fatal flaw, but there are techniques to address those. So if you can address some of that? Have you done any of that? And also, any small studies where you can measure those unmeasured confounders if they were so important to do so? I wonder what was the rationale on any of that has been done?

Rita-Ouellet-Hellstrom: Are you asking Dr. Sidney or us?

Enrique Schisterman: Dr. Sidney.

Stephen Sidney: No, we haven't done that. We could, though I don't know what it would look like, because I don't know how much -- for how many people we have the data in association with their contraceptive use. As I indicated before, for a subset of this population, we will have smoking data. We will have BMI data. It will vary over the time, where more recent years there would more of it available. We have race, ethnicity for maybe two-thirds of it, but we haven't done any of those analyses at this point, no.

Enrique Schisterman: But for a sensitivity analysis, you don't need any new data at all.

Stephen Sidney: Uh-hm. Well we haven't done that. We were quite pressed to get done what we got done.

Enrique Schisterman: Okay.

Julia Johnson: Dr. Raymond? No? Dr. Morrato?

Elaine Morrato: Thank you. My question is for Dr. Sidney as well, and I'm trying to better understand a bit more of the case validation and then the issue of what might be referral or diagnostic bias and whether or not there's any data in the information that you have that can shed some light. So you clarified again that there was an 89% validation rate for the outpatient DVT. Could you just quote for the sake of us all hearing at the same time, the rate for the hospitalized events?

Stephen Sidney: I don’t have that on the top of my head. It can be calculated. It's actually lower than that for the hospitalized cases, and it's quite a bit dependent on site. It was much higher at the Kaiser Permanente sites than from the Medicaid sites.

Elaine Morrato: Okay. So by lower --

Stephen Sidney: That means we reviewed a case. It didn't meet the criteria for --

Elaine Morrato: Right.

Stephen Sidney: -- being (inaudible).

Elaine Morrato: The sponsor's quote a study and it may not be directly comparable, but they quote a study that only 20% of women that are referred for VTE evaluation ultimately have a diagnosis. Would us say that the lower rate is of that magnitude or you're going from like 89 to 70 (inaudible)?

Stephen Sidney: No, the overall is going to be somewhere 70ish, perhaps somewhere like that. At Kaiser Permanente's I think it's around 90ish or so, 80 to 90 range.

Elaine Morrato: Okay. Yeah. So then the sponsors talk about the relatedness between the VTE diagnosis and the referral diagnostic. I'm wondering -- I understand that you used a threshold of hospitalization as the criteria for the case. Were you able to look at the records to see how many folks actually had maybe the diagnosis that just didn't meet the criteria of hospitalization, to get some sense of was there a differential referral bias in terms of leading to hospitalization and workup?

Stephen Sidney: No. I mean I think for acute myocardial infarction, most people who have acute myocardial infarction are going to be hospitalized. For VTE, are you talking about venous thromboembolism?

Elaine Morrato: Yes. Sorry.

Stephen Sidney: Well yes, by looking at the outpatient diagnoses, I mean that would -- I mean if it doesn't get a diagnostic code, we're not going to see it.

Elaine Morrato: Okay. So is it proper then to compare the 20% study that's being quoted with what you're finding in yours? It's truly 89% is the validation for outpatient?

Stephen Sidney: Well maybe a bit lower than that, but not nearly as low as 20%. I'm sorry. The other thing, let me just explain, there's another factor that I don't have the numbers on the top of my head on this. We required the diagnosis in conjunction with prescription for an anticoagulant. And I can't actually tell you what the number would be if you didn't have that and that would probably get into more of -- you know, much lower.

Elaine Morrato: Right. That might be informative to have at some point.

Stephen Sidney: Uh-hm.

Julia Johnson: Thank you. Dr. Hoeger?

Kathleen Hoeger: Yes, my question is for Dr. Sidney also. Regarding OC starts, particularly in the new users, there's considerable data that women switch frequently within the first two to three months and then are on a second -- a different oral contraceptive for various concerns. How is that handled in this study? And if they switch to one that wasn't in the comparator group, what would happen to that patient?

Stephen Sidney: For the -- you know the cleanest analysis is the new user one. So the new user one would end at the end of their first use, basically, and the analysis would account for that. If they're in the all user analysis, then that exposure would end at that point and if (inaudible) went to another study CHC, another would begin. If they went to a totally different CHC, that wouldn't count, but it would be included in calculating start and stop dates.

Julia Johnson: We have three more committee members who have not yet had a chance to ask questions, so we're going to go with those three and then we will proceed with our break. Dr. Gardner? Okay. Dr. Wolfe?

Sid Wolfe: This is for Dr. Sidney and Dr. Hellstrom. In Figure 8, not labeled, but the distribution of covariates for all sites by study, CHCs (ph) and new users. You showed and pointed out that if anything, the risk factors ranging from use of drugs to hyperlipidemia were lower in the Yasmin group and I assume that part of that is to be accounted for on the basis that it was a younger group. If that is not correct, please tell me.

But the further question is there are a number of disease states, cancer comes to mind, which are themselves risk factors for VTE, and was there an effort in both your study and in some of the other studies, particularly the ones that do not seem to find increased risk, to exclude cases which were not "idiopathic" cases for VTE, because if you didn't do that or if anyone who did research on this didn't do it, it would tend to reduce the risk ratio by adding cases that are known to be associated with causes other than the use of drospirenone. Can you just comment on that, please?

Stephen Sidney: I think Rita can more generally comment, but cancers were excluded from our --

Rita-Ouellet-Hellstrom: Actually, Dr. Wolfe, it's the opposite. The studies that did include all women on contraceptives, like the EURAS study and i3 showed no risk, whereas all the other studies excluded women with cancer. Some excluded women --

Sid Wolfe: That's where my question was going. That if you didn't excluded them, which you did in the Kaiser study, you would tend to decrease the possibility of a risk ration because you're adding non-idiopathic cases that would go across.

Rita-Ouellet-Hellstrom: Well, as I said, the EURAS study and i3 studies were the ones that did not exclude women, but the i3 did match expose propensity.

Sid Wolfe: Thank you.

Julia Johnson: And finally, Dr. Hennessey?

Sean Hennessey: Thank you. This is a question for Dr. Sidney as well. So there have been some prior studies showing that these desogestrel is associated with a higher of VTE compared with levonorgestrel. Did you look at desogestrel in your study?

Stephen Sidney: No. No, we didn't.

Rita Ouellet-Hellstrom: May I? The objective for the FDA study was to try to compare Yasmin and the newer products to what was used most frequently in these datasets. And therefore, desogestrel was not one of products used frequently.

Sean Hennessey: I understand. It may have been informative if that were treated as a known positive to see the ability of this assay to identify a known positive, for example. Or if we think that it's a feature of the newest OC out there has the highest risk, then desogestrel's no longer the newest one, so that risk would have gone down, for example.

Julia Johnson: And Dr. Raymond, an opportunity for a question.

Elizabeth Raymond: Thanks. Can you remind us, Dr. Sidney, what proportion of the VTEs were outpatient?

Stephen Sidney: They were about one-third.

Elizabeth Raymond: And can -- I think it might be useful to have an idea of the clinical picture of these VTEs. Obviously few of the women actually died, but can you give us an idea of what did happen with these women or what typically would have happened with these women?

Stephen Sidney: You know it wasn't the purpose of the study go through their clinical course. By and large if they were hospitalized, they were diagnosed, treated, and discharged and followed afterwards.

Elizabeth Raymond: And generally they recovered? Presumably?

Stephen Sidney: We did not go beyond diagnosis. It wasn't the purpose of the study beyond the diagnosis and verifying it.

Julia Johnson: Well thank you to the FDA and our guest speaker for answering these questions. We will have time for additional questions to be asked in the afternoon, and I would thank all the members of the committee to keep those questions. They're very important and we do want to hear them this afternoon. Now we are going to take a short break. Panel members, please remember that there is to be no discussion of the meeting topic during the break amongst ourselves or amongst members of the audience. We will reconvene at 10:15 in nine minutes.

(Break)

Julia Johnson: Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency as the advisory committee meetings, FDA believes that it is important to understand the context of an individual's presentation. For this reason FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria and interests in the sponsor, including equity interests and those based upon the outcome of this meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

John Talian: Thank you, Madam Chairman. My name is John Talian. I'm Vice President, Regulatory Affairs for Bayer HealthCare Pharmaceuticals. On behalf of Bayer, I'd like to thank the FDA and the members of the advisory committees for the opportunity today to discuss the complex scientific matter venous thromboembolic events associated with the use of combination oral contraceptives.'

Bayer has had extensive meetings and communications with the FDA concerning safety and efficacy of drospirenone-containing COCs over the past 15 years. The main focus of our discussion today is a group of observational studies that vary in their results concerning differential risk of VTE. We will discuss the methodologies used in these studies, as well as the strengths and limitations of each. Based on all of the available evidence and our examination of the data, Bayer's position is that the totality of the data support a favorable benefit risk of drospirenone-containing COCs when used according to the product label.

This first slide depicts the regulatory history of our products in the U.S. Yasmin was initially approved in 2001, followed by Yaz in 2006, with the two secondary indications approved in 2006 and 2007 respectively. The folate containing products, Beyaz and Safyral were approved in 2010. The development history is shown here. Several thousand women were enrolled in the initial clinical studies to support

approval. Tens of thousands of women participated in post-approval studies that were designed and conducted following consultation and review by U.S. and Europe health authorities.

Dr. Plouffe will discuss these post-approval studies followed by Dr. David Grimes examination of the observational studies. Dr. Makuch will discuss the FDA funded study, and Dr. Lukes will present a clinician's perspective on patient counseling and choice of contraception. Dr. Plouffe?

Leo Plouffe: We appreciate the opportunity to review with the committee and the FDA the post-approval safety studies from Bayer. And just to highlight some of the information already presented from the FDA, as an OB/GYN clinician and also a researcher in the field of women's health, VTE are clearly a rare, but also serious event. They affect non-COC users, COC users, and they also have an increased risk during pregnancy. There's no evidence that the course of VTE is altered in any of these states. So there's always the risk of deep venous thrombophlebitis or pulmonary embolism in these events. And clearly, while fatality rates are low, there can be fatalities in any of these groups.

Right from the launch of Yasmin, the timing of the launch of Yasmin came at the aftermath of a lot of controversy around the risk of VTE with COC during the 1990s. And that risk was first looking at progressively lower doses of ethinyl estradiol in the pill, as well as different progestin coming forth in the marketplace. And in light of these debates, especially from the onset, the EMA wanted to initiative a study looking at the rate of VTE with a new preparation, Yasmin, compared to other oral contraceptives.

Similar thoughts came through in Ingenix study which we'll discuss in a second. Out of the studies that were done in the 1990s, there are a number of elements that came to light that must be included in high quality studies to try to answer the risk of VTE among different COCs. Some of these are basic sound principles of observational studies such as having a protocol, amendments, and a full statistical analysis plan prior to initiating data analysis. Reproducible methods yielding reproducible results is also a critical element. And then the principle of demonstrated comparability among treatment groups on key risk factors. And then depends on the availability and the accuracy from the data sources.

In addition to these general principles, certain key principles came to light specifically when comparing VTE across different COCs. And these have to do with biases that have to be considered and these include duration of use, pattern of use, attrition of susceptible and healthy user effects, prescription bias or channeling, the validity of diagnosis for VTE, and the referral diagnostic bias for VTE and many of these elements have already been discussed this morning as key elements to consider in conducting studies comparing the risk of VTE across COCs.

So if we now focused on post-approval safety studies with Yasmin conducted by Bayer, looking specifically at venous thromboembolic event there are a total of four studies that we've referred to in our briefing document. The Ingenix study, which was a post-approval commitment to the FDA; the European Active Surveillance Study or EURAS, which is a post-approval commitment to the EMA; then there were two additional voluntary studies by Bayer. One was an additional five years of observation to the EURAS study, so called the long-term active surveillance study or LAST study

and there was another voluntary commitment undertaken in Germany, so called the German Case Control Study. And I will go through each of these studies individually.

In the FDA briefing document there was reference made to the prescription event monitoring study, which is actually a non-comparative surveillance program conducted in the U.K. and internally, we've never considered this to be truly a study, so we did not include it our briefing document. We'll be glad to discuss these further if the committee has questions.

In terms of the Ingenix study, at the launch of Yasmin there were significant concerns on the part of the FDA related to the antimineralocorticoid activities of Yasmin. It's acknowledged in the label that it provides a dose comparable to 25 milligrams of spironolactone. And because of this, there was an interest in establishing a post-commitment study that would monitor any adverse event related to the antimineralocorticoid activity. The sponsor looked for a group with whom they could collaborate to actually conduct the study, and the Ingenix Group was selected at the time, because they had access to the United Healthcare database, one of the largest healthcare databases in the U.S.

The Ingenix Group is who designed the protocol in extensive discussions with the FDA and the sponsor. The protocol was finalized and then shared with the FDA before the start of the conduct of the study. During the entire conduct of the study, interim reports were also shared with the FDA. In about mid-2003, in light of the conduct of EURAS study for VTE, the FDA also expressed its interest of looking at VTE in the context of the Ingenix study. There were extensive discussions again, primarily driven by the investigators at Ingenix about the challenges of converting initially a study looking at antimineralocorticoid activity and converting into a VTE study.

However, it was agreed that this could be done, but there were two separate validation studies that were conducted to make sure that risk factors such as BMI, such as smoking, that were not initially considered or available in the database, could have been accounted for by the propensity score methodology used to create the Ingenix cohort. These validity studies ultimately yielded information that supports the idea that the propensity score matching was overall effective and therefore is valid in assessing the outcome of VTE.

The final reports of all the studies from the Ingenix study were shared with the FDA in 2005 and publications occurred in 2007. Now briefly to review the Ingenix study design, therefore it's a U.S. claims based observational cohort study. It enrolled over 67,000 women and generated a follow-up of 41,656 woman years. Women were assigned to either Yasmin or other COC (inaudible), all other COCs in use at the time in the U.S. Very important to reminder that the Ingenix follow-up was of 7.6 months. So essentially, the majority of the cohort are first year users.

While there were several outcomes identified in the protocol, I will focus on the VTE for this presentation. Allow me, however, to add that the exploration around the antimineralocorticoid activity of Yasmin that was conducted in the Ingenix did not reveal any patterns of concern. So all the adverse events were aligned and there was no difference with the other preparation being considered. And again, we'll be glad to share these data more in detail later. The cohort creation was initiated in the United Healthcare database which covered at the time, over 15 million lives, almost a million women, and from this group they were looking at dispensing of OCs and ultimately the cohort was formed with a 2:1 matching using propensity score to match the cohorts.

So for each Yasmin users, there were two individuals in the other cohorts of OCs. Each case of VTE was validated through an actual clinical chart review. So cases were flagged in the database, but there was actually a clinical chart review and case adjudication was conducted by a reviewer blinded to exposure. There are a number of strengths of all the studies including the Ingenix study. We listed the number in the briefing document. Allow me just to highlight a few here. So the VTE confirmation in the Ingenix study was based on the clinical chart review and blinded adjudication.

The balance of the cohort was insured through propensity score matching, and in the case of VTE, there was further validation study. And then the cohorts were matched based on pattern, timing, and duration of exposure. In terms of limitations, clearly there's potential here for referral and diagnostic bias when it comes to VTE. There's no direct adjustment for BMI or smoking, even though that was attempted and successfully confirmed through the validation study. Then we're unable to distinguish here between first ever starters versus new start or restart, and that has already been identified this morning as one of the challenges of working in databases.

The results of the Ingenix study are that the risk of Yasmin is similar to all the other COCs studied in the Ingenix cohort. Now if we turn to the EURAS study, as I stated already, the EMA from the onset of launch of Yasmin because of the aftermath of what they refer to as the second versus third generation situation in Europe, were interested upfront to monitor the situation with a new onset pill. Bayer at the time looked for collaborative group and there was already an international effort underway to set a prospective cohort study to look at various -- the risk of VTE between different COCs.

This was an international effort. Dr. Walter Spitzer from Canada was involved who's known to many individuals. Ultimately, the investigative group who could conduct the study, was the Center for Epidemiology and Health Research which is based in Berlin. This came to be known as the EURAS study. The protocol was entirely designed by that group with input from the EMA and the sponsor. The protocol was finalized and shared with the EMA and regulators around the world. During the conduct of the study, interim reports were provided at regular intervals and then the final report was generated in 2006 with the seminal publication in 2007.

The EURAS study is a multinational prospective non-interventional controlled cohort study. It enrolled 58,674 women and yielded over 142,000 woman years of observation. There were a number of cohorts in the study that were followed and the follow-up in the study ranged from 1.5 to 5 years. There are several outcomes identified in the protocol both as primary and secondary endpoints. We'll focus four on VTE.

The source population from EURAS were women considering contraception in seven European countries. The oral contraceptive cohort was assembled by women meeting with their clinician and selecting which form of contraception appealed to them the most and which specific oral contraceptive they elected to use. Once that choice had been made, they were offered entry into the study and if they chose to participate in the study, they signed an informed consent. Depending on the choice that had been a priori made as to which oral contraceptive, women were then assigned to either the Yasmin cohort, levonorgestrel cohort, or other oral contraceptives.

The process to confirm VTE again was based on a clinical chart review of the subjects and ultimately, adjudication by three reviewers blinded to exposure. Again, there are a

number of strengths and limitations to the EURAS study. On the strengths side, it was adjudicated for predefined confounding factors, including age, BMI, personal and family history of VTE. It's a prospective design which therefore allows to inherently control for duration, pattern of use, and through a questionnaire was able to actually ascertain first time ever users.

The VTE cases were confirmed by both chart review and blinded adjudication. On the limitations side, the EURAS depends on patient self-reported questionnaire. They complete a questionnaire initially at the study site and then every six months they're sent a questionnaire they must fill out. So there's always in this situation, the potential that recall of events may be influenced by memory. On the other hand, individuals know that every six months they will be asked to fill out a questionnaire about health events in their life. And so in that context, they may be paying more attention to these events to make sure they report them at the time they fill out the questionnaire.

Last but not least, inclusion in the study does require patient consent and obviously that can attract certain types of patients more than others. The results from the EURAS study are presented here showing the results for Yasmin compared to levonorgestrel EE combination oral contraceptive, as well as Yasmin to all other oral contraceptives included in the study. Again, the conclusion here is that the risk of VTE is similar either to levonorgestrel or to all other OCs included in the EURAS study. As I mentioned earlier, at the completion of the EURAS study, Bayer voluntarily undertook conducting a study to generate an additional five years of observation.

And this five years extension of the EURAS trial is referred to as the LASS extension. Of the original group of 58,674 women that took part in the EURAS study, 47,799 agreed to be reconsented and therefore be followed for an additional half to five years of observation. When I'll be referring to results from the LASS study, we're really looking at the totality of the data generated between the EURAS and the LASS period, so it's over a period of 10 years and it's important to remember that this is an observational study.

So while we don't rule out that one woman may have been on the very same pill from day one of EURAS all the way through to the end of LASS, we're generally looking at women who stop and start using contraceptives and you may go from one preparation to another. So that's an important element of this observational study. Ultimately, the LASS study, both EURAS and LASS, yielded over 318,000 woman years of observation and over 216 woman years of OC exposure.

And I think it's important at this point just to take a second to acknowledge that this was only possible through the dedication of the women who agreed to sign a consent and participate in the study. So for many women, this was over 10 years of regularly filling out questionnaires, answering our questions for clarification, being in contact, and I think these women have really made a tremendous contribution to the field of women's health and to the field of contraception.

The strengths and limitations of the EURAS and the LASS study, very much are similar to the EURAS study. For the sake of time, I will not repeat them. The results from the LASS study, so the combination of EURAS and LASS, show that the risk for Yasmin is similar to levonorgestrel and the risk for Yasmin is also similar to levonorgestrel and other OCs. Now the data presented here are as treated analyses. I just want to point out that we've also conducted additional analyses intent-to-treat per protocol, all of which align with these results.

We also conducted a subset analysis of idiopathic only cases, and again the results very much are aligned with these results and we'll be glad to share these later. The German case control study was a voluntary commitment from Bayer around an oral contraceptive that Bayer recently had introduced in Germany which is a combination that is not available in the U.S. as a combination, but it combines deniogest and ethinyl estradiol known as Vallette. But at the same time as the study was being designed, it was decided that a secondary, predefined secondary objective of the study was to compare Yasmin to levonorgestrel COCs.

Now it is a case control study and ultimately the odds adjudicated ratio of the study show a risk of 1.0 comparing Yasmin to LNG COC. So if we look at all the Yasmin post-approval safety studies so far conducted by Bayer, the Ingenix and EURAS study were both post-approval commitment studies and both of these show a risk similar for Yasmin compared to the comparator OC in the respective studies. The LASS study and German case control study were further voluntary commitments from Bayer. The risk is similar in these studies compared to other OCs.

Now we heard today, the interest in arterial thromboembolic events and indeed this interest is longstanding in the area of oral contraception. Right as the studies were being designed for the Ingenix, the EURAS, and the LASS study, ATE as a predefined outcome was something that was included in the design of the studies. In case of the Ingenix study, there ultimately turned out to be one ATE in the Yasmin cohort and three ATEs in the other OC cohort. So clearly these results do not give rise to any concern, but also fairly limited in the ability to draw significant conclusions.

In the EURAS study, ATEs were also looked at and the initial look at the EURAS study at the completion, suggested that there may be actually a lower rate of arterial thromboembolic event seen with Yasmin compared to other preparation. There are a number of underlying reasons that may drive this, included the antimineralocorticoid activity seen with drospirenone. So ultimately, the long-term active surveillance study, the LASS study, including also looking at ATEs for that, and I'll purely present here the results from the LASS study, since they encompass both the results from EURAS and LASS.

Arterial thromboembolic events were recorded as serious adverse events during the entire conduct of the EURAS and the LASS extension. Clinical chart review was undertaken for any serious adverse event. And ATEs here were defined at acute myocardial infarction, stroke and transient ischemic attacks. The results from the LASS study show that compared to Yasmin, the point estimate is 0.04 with an upper confidence interval of 0.9.

Results for Yasmin versus other OCs including levonorgestrel is 0.4 with an upper confidence interval of 0.8. As has been already highlighted by the FDA, the numbers when it comes to ATEs are much smaller given the age of the population and all the factors. We do think that these results though are reassuring in terms of the risk of ATE associated with Yasmin.

If we now turn our attention to post-approval safety studies with Yaz. Upon the completion of the EURAS, and in fact the EURAS study was able to be completed with less than 3% loss to follow-up during the conduct of the EURAS. There was a convergence that a study like EURAS could actually be conducted on a broader scale, on an international scale. And so therefore, as part of the post commitment to looking

at the situation of VTE and the VTE risk with Yasmin, the commitment was made both to the FDA and to the EMA to conduct the International Active surveillance Study, other known as INAS.

The outline of INAS is very similar to EURAS, but this time it includes U.S. sites as well as European sites. It has completed enrollment and it has enrolled 85,260 women and it's expected that the completion of the INAS OC trial to yield over 200,000 woman years of observation. The follow-up is planned for two to five years. And again, there are several outcomes. We'll focus here on the VTE. The source population for INAS is a very similar concept construct than in EURAS, except this time it includes women in the U.S.

Again, the choice of the oral contraceptive is left up to the woman and the clinician, and once they choose which contraceptive they want, they're offered entry into the study. They sign the informed consent. They fill out the baseline questionnaire. Then they engage in filling out the questionnaires every six months. In the INAS OC study, we have a Yaz cohort, a Yasmin cohort and another oral contraceptive cohort. And we have defined a secondary endpoint of levonorgestrel COC within that other oral contraceptive cohort.

The strengths and limitations of INAS overlap those already outlined for EURAS. So again, I will not repeat them for the sake of time. The data for INAS at this point are interim results and these are based on the last interim that has been shared with the FDA as a full interim report which dates back to February 28 of this year and the risk of VTE for Yaz is similar to the other OCs in the study.

Now as was already highlighted this morning, there have been a large number of publications in this area, especially over the last few years. I've highlighted for you here the data and the information around the EURAS study, the Ingenix study, the German case control study, and the LASS study. And all of these studies here really are focusing on Yasmin. Dr. Grimes and Dr. Makuch in their presentation will present an overall analyses of these study strengths and limitations.

Based on the data so far and the evidence available through the conducted post-approval commitment study, the risk of VTE with Yasmin is similar to other COC study. These include the data generated through the Ingenix, through the EURAS and LASS, through the German case control study. The risk of ATE with Yasmin is similar than other COCs studied. And the risk of VTE with Yaz based on interim data is similar to other OCs studied. And again, I want to highlight, these are interim data.

At this point, I'd like to turn the podium over to Dr. David Grimes. Dr. Grimes is one of the few individuals who double boarded in obstetrics and gynecology, as well in the field preventive health, and he's also a member of the Institute of Medicine. Dr. Grimes?

David Grimes: Good morning. I'm going to review the nine published observational studies that deal with this issue. In terms of disclosure, I serve on the Data Safety Monitoring Board of the ongoing INAS trial and I've been paid for my participation here today. However, I have no financial interest in any pharmaceutical company and no vested interest in the outcome of these proceedings.

This morning, I'd like to describe for you a simple four-point checklist for evaluating observational studies. I'll explore the evidence for prescribing bias and differential

misclassification, and finally summarize the relationship between study quality and study findings. All published observational research has residual bias. The only way to avoid that is to do a randomized controlled trial. So when we encounter published observational reports, we need to consider the following questions.

First, is there selection bias? That is are the two groups comparable at the starting blocks. In a cohort study, that means that the exposed and unexposed should be similar in all important respects except for having or not having the exposure. In the case control study going backwards in time, the cases and controls should be comparable in all important respects except for having or not having the disease. An example of selection bias would be comparing heavier women on Pill A with lighter women on Pill B.

That would not be comparing like with like. Second, is there information bias? Have we gathered information about both groups in just the same way? In a cohort study going forward in time, this means we've gathered information about outcomes for the exposed and unexposed similarly. In a case control study going backwards in time, have we gathered information about exposures in just the same way? Now an example of information bias in a control study would be gathering information from cases by a beside interview after surgery and gathering information from controls by telephone interview.

Third, as mentioned by Dr. Montgomery Rice this morning, confounding is an important question to ask. Confounding is a mixing or blurring of effects. We think we're measuring the relationship between an exposure and an outcome. We're actually measuring the impact of a third factor in the mix. Back in the 1970s, we thought that birth control caused a large increase in the risk of MI. It turned out it was due to the fact women who chose to use OCs, were more likely to be smokers than were other women.

So after considering these three biases, one should stop and say, well can I explain away the results of this study. Oftentimes, the answer is yes. If not, then and only then does one go on to look at the likelihood of chance. Now the five potential biases that Dr. Plouffe mentioned earlier fall into the first two of my category checklist. Duration of use, attrition of susceptibles and prescribing bias, also known as channeling, are types of selection bias; imbalance at the start. The validity of diagnosis for VTE, especially differential is concern for information bias. And finally, referral or diagnostic bias is a stubborn kind of information bias in studies of this type.

Now here's the chronological listing of the nine published observational reports to date. You've heard already about the EURAS and Ingenix study. In 2009, Lidegaard published a study out of the Danish patient registry. The next study was the MEGA case-control study done as a case control out of coagulation centers in the Netherlands. And you've heard about the German case control study. Then just this year, we've had several publications in the BMJ and elsewhere: the Jick study, which was a nested case control study from a U.S. administrative database; the Parkin study, another nested case control study in a British administrative database; a reanalysis of the 3009 Lidegaard report; and most recently, another administrative database, Klaylet (ph) out of Israel.

Here I've plotted for you the point estimates and 95% confidence intervals from these nine studies. You can see that some hover along one, meaning no association; some are in the range of two and smaller; and only one is as far as three -- the Parkin study

which has a very wide confidence interval due to sparse numbers. Given nine studies with some complex approaches and five potential biases to consider in each, I need to start at this point with an apology to my epidemiology colleagues around the table for what will be, of necessity, and incomplete and superficial treatment of these complex issues.

In the interest of time, I'll focus on just two -- prescribing bias and validation of VTE as an outcome. As mentioned by the FDA this morning and by Dr. Hillard and others, prescribing bias is an important concern in studies of this type. What this means is that women at increased risk of VTE are preferentially being prescribed Yasmin or other drospirenone pills. We do have empirical evidence, objective evidence from the EURAS study, that this indeed has occurred. In the EURAS study, women who were obese were 60 to 80% more likely to be prescribed Yasmin than other birth control pills.

And we know that obesity itself is an independent risk factor for VTE. The result is what's called confounding by indication. Now in the EURAS study, the amount of bias was small and it would have only a marginal effect on the point estimate, but it was in the expected direction. I'd like to introduce you now to a term that I'll use in the following two slides and this is calculation of what's called a preference ratio used in surveys in the 1990s. They would query a random sample of physicians and ask them, given this risk factor, such as obesity, what would be your pill of choice?

For example, if 60% of physicians said, I choose a third generation pill, and 30% said, I'd choose a second generation pill, and 10% had no preference, you'd use the second generation as the referent group and simply divide 60% by 30%. That yields a preference ratio of two which can be thought of as a relative risk. So given obesity, a physician would be twice as likely to prescribe a third versus a second generation pill. Now with that as background, let me share with you two important surveys done in Europe during the 1990s.

The first survey was done in Germany, and given obesity, German physicians were twice as likely to prescribe a third versus second generation pill. You can see that the preference ratio ranged from two to four depending on the risk factors. But the evidence for prescribing bias is even stronger in the same study done in U.K. Given obesity, physicians in the U.K. were 17 times more likely to prescribe third versus second generation pills. Going up to a combination of factors for which it was almost 60-fold.

In summary then, we have empirical evidence from the EURAS study and physician surveys, two of which I've described and one by Bitzer (ph) in Switzerland looking at estrogen dose, all of which corroborate the prescribing bias is ongoing. Now with regard to the Ingenix study, what did it avoid to do to avoid these types of biases? With regard to duration of use, they studied new users only. With regard to attrition susceptibles, they had a complex propensity matching score with over 100 covariates to try to ensure comparable cohorts. The same was used to control for prescribing bias.

With regard to validity of diagnosis, there was a clinical chart review and adjudication by blinded reviewer. But importantly, in all these studies, referral or diagnostic bias cannot be excluded. In the EURAS study, duration of use was controlled for by having analysis by groups based on duration of use and pattern of use -- new users, switchers, and repeat users. Attrition of susceptibles was dealt with by analysis by groups based

on history of prior use. Prescribing bias was accounted for by having extensive information at baseline, before exposure about (inaudible) confounding factors.

In terms of validity of diagnosis, there was a clinical chart review and then adjudication by blinded reviewers. But again, referral and diagnostic bias cannot be excluded here. I'll just briefly mention the Dinger case control study which Dr. Plouffe described earlier, a well done case control study in Germany. Controls were randomly selected from the neighborhood, blinded adjudication to VTE, and good control of both personal and family confounding factors in the analysis. And again, it found no increase in the risk with Yasmin compared to other pills.

I trained as an epidemiologist at the CDC in the 1970s in the epidemic intelligence service. And there we were all impressed with the importance of confirming that the exposure had occurred and also that the outcome had occurred. Now in the observational studies I've just described, the first criteria is generally well met, but increasingly, the second is not, for unclear reasons. And this is of concern because the type of misclassification influences the effect on the results. If one has random misclassification, just noise in the system, that tends to drive the relative risk or odds ratio toward unity, obscuring an effect that might be real.

In contrast, the misclassification is generally directional, non-random, systematic, and generally spuriously elevates the seen relative risk or odds ratio. Now it's been known in epidemiology for decades that one simply must confirm that the outcome has occurred. Indeed, Susan Jick who's a co-author on two of these papers, published in The Lancet back in 1997 and I quote, "Unless one examines clinical records it is impossible to ascertain whether a case of VTE has been documented by diagnostic tests. That is where there is in fact a case."

But more important for our consideration today is the following. In February of this year, the FDA published draft guidance on validation of outcomes for database studies. And I quote, "Because electronic administrative claims data are not collected for investigative purposes, but rather for patient care or reimbursement purposes, it is vitally important," I repeat, "vitally important to ensure that medical outcomes of interest are validated." And they cited Lanes (ph).

Over the past decade the number of poor studies from administrative databases submitted to obstetrics and gynecology and other journals has been a problem. Indeed, several years back the editor of Obstetrics and Gynecology invited me to write an editorial cautioning readers about the serious limitations of administrative database studies used for epidemiology. In the process of writing that, I looked at the studies done to validate diagnoses in the Danish registry and it was variable. For some diagnoses, they were very accurate, and for others like VTE, very poor.

In response to my editorial, Dr. Lidegaard wrote back that, and I quote, "We have the opportunity to link the discharge diagnoses with those who are anticoagulated after the diagnosis," thus validating his words. Each case from this simple merger of data. That's not validation. That's a diagnostic algorithm. But ironically, by that time, the validation had already been done independently. Another group of investigators in Denmark, looked at 1,100 medical records of patients 50 to 64 years of age in that database with a diagnosis of VTE. They found that 452 of the 1,100 were not VTE.

Stated alternatively, 41% -- 41% of VTE diagnoses in the Danish registry are not VTE. And this ranged from 25% of patients diagnosed on the ward to the majority of those

diagnosed in the emergency department. And here was the summation of these Danish investigators from (inaudible) in Copenhagen, not skeptics in America like me, but Danes announcing to the world's epidemiology community that these data should be used with caution. That diagnosis of VTE is suspect in that database.

Well interestingly in the reanalysis just published this year of the 2009 Lidegaard report, two physicians blinded to exposure audited 200 randomly selected VTE cases from the Lidegaard study. And they found that 26% of the ward diagnosed cases were not VTE, despite Lidegaard's prior assertion in 2009, that there was no more than 10% misclassification. And this is strikingly similar to the 25% found independently by Severinsen and others in their 2010 audit.

But for me as a reader, the persistent problem with the Lidegaard 2009 and 2011 is the fact that it compared women who could not have started a drospirenone pill before 2001 when it was introduced, with women who could have started a levonorgestrel pill in 1994 or even earlier. Now as Dr. Sidney said this morning, the cleanest comparison by far is first ever users. And in the analysis submitted to the EMA this comparison was made and relative risk for Yasmin versus levonorgestrel pills was 1.2 with confidence limit that widely overlaps one.

For unclear reasons, this analysis did not appear in the BMJ publication this year. So here are the nine studies listed by whether they did or did not validate the outcome of VTE and you'll see in green that the studies which validated the outcome found either no increase in the risk or an insignificant increase in the risk of VTE. In contrast, the other studies, which did not validate the outcome of interest, all found an increased risk. Stated alternatively, every single published report that has found a significant increase in the risk of VTE was an administrative database study that did not meet the FDA's published standards for evidence quality. That's telling. Research methods matter.

Finally, we still have (inaudible) of both referral bias and diagnostic bias. Because of news media attention, women with vague complaints or leg complaints are more likely to seek care, and once reaching a healthcare facility, they're more likely to have an expensive diagnostic evaluation. For example, in the EURAS study, 18% of women referred had confirmation of the VTE diagnosis compared to 25 or 26% of women using other pills, indicating that more worried well women were getting into evaluation with Yasmin than with other pills.

Well what drives these biases? This sort of attention. As early as 2002, the BMJ was warning physicians based on sparse data that these pills were dangerous. A brief mention of the MEGA case control. I've been reading case control studies for four decades, but I can't recall one like this. Forty-one percent of controls were spouses of cases; the rest were random sample over the population. Now controls in a case control study should be women who are representative of those at risk of having the disease and spouses of cases are hardly likely to be representative of Dutch women at risk of having a VTE and their contraceptive practices are likely different as well.

In addition, there were uncontrolled confounding problems and despite these problems, they found no significant increase in the risk of VTE. So here are some of the unresolved issues. In the Lidegaard study, we had extensive misclassification of VTE and inadequate control for potential confounding. In the MEGA study, we had an improper control group and again inadequate control of confounding. In the Jick American database study, we had no case validation and they purged through an

unclear process, non-idiopathic cases. Even more troublesome is the British administrative database study who did the same problems plus a very peculiar finding.

There were 61 cases of VTE in the Parkin study. Thirty-four were pulmonary emboli and 27 deep venous thrombosis. Now I'd ask any of the clinicians around this table, have you ever seen that in clinical practice? Can you imagine the scenario that has more pulmonary emboli than deep venous thrombosis? This is completely implausible and robs any clinical credibility from that study from my perspective as a clinician. And finally, the most recent entry was the Israeli database study which again lacked validation of the diagnosis and incomplete control of confounding.

So if we look to the better studies, we see that we have a prospective cohort study, we have a database study, we have a case control study, all of which confirm the diagnosis and all of which found no increase in the risk. In conclusion, the literature on VTE risk with drospirenone pills is inconsistent, but this is easily explained by the varied study designs and inadequate control of bias. Prescribing bias or channeling and information bias readily account for these weak associations. The more recent studies, especially those this year, did not compare like with like, a fundamental flaw.

And as you've seen, the studies with more rigorous methods show no greater risk of VTE with drospirenone pills than with other oral contraceptives. Next, I'd like to introduce Dr. Robert Makuch from Yale University. He's a Professor of Biostatics and also heads the drug regulatory curriculum there. He's going to address the FDA study. Dr. Makuch?

Robert Makuch: Thank you. My disclosures are as follows. A paid consultant to Bayer HealthCare Pharmaceuticals and I have no vested interest in the outcome of this meeting. The objectives of my presentation are described here. Brief remarks regarding the FDA funded study, first phase. Assess this study in terms of its design, conduct, analysis and interpretation. Third, describe its limitations and strengths, and finally, to provide some overall conclusions.

We've heard about the study objectives of the FDA funded study, Phase I. I will not repeat it here. Also, we are fully aware of the access dates July 2000 through December 2007, and you've heard a description previously of the four sites. The control groups and the Yasmin group are denoted here along with the ethinyl estradiol doses uses. For Yasmin it is 30 micrograms. The primary comparator group is a combination of three different contraceptives ranging from 20 to 35 micrograms of ethinyl estradiol, including 30% of subjects on the COCs containing 20 micrograms of ethinyl estradiol.

And of course, you've heard previously, the dose relationship of this to VTE. And finally, the subsequent comparator group subset of the overall COMP group of 30 micrograms of ethinyl estradiol, denoted as the LNG 2 group. The endpoints have been prescribed previously. VTE inpatient and outpatient, arterial thromboembolic events, both acute myocardial infarction and ischemic stroke. And finally, mortality, both all-cause as well as cardiovascular mortality.

I chose to use two guides to assessing the FDA funded study. The first was the guidance for industry and FDA staff, best practices for conducting and reporting pharmacoepidemiologic safety studies, the draft guidance coming from the FDA in February of 2011, and secondly, guidelines for good pharmacoepidemiologic practices or GPP, published as noted.

I should say before I now will go my review of the study, that first this is a tremendous effort undertaken by the FDA and the investigators. So it is certainly data that must be considered very carefully. Secondly, my comments should be taken in the context that this is the first phase of the FDA funded study. You've heard this morning and also in their documents that there is a second subsequent study being considered. And thirdly, the comments I'm going to make are not limitations for this one study only. They are limitations that as you've heard earlier, apply to a wide variety of the studies that you will have in front of you for further discussion today.

So first, I always like to see a protocol and so a scientifically valid study protocol should be developed by predefining certain elements related to the design analysis conduct and reporting. In bold print, as it was in the draft guidance document from the FDA, all of the elements described within this guidance should be addressed in the protocol. Secondly, the GPP highlights several critical factors including providing a written protocol with dated amendments and justifications. For my review, no protocol was provided until yesterday, December 7, and so I will not provide a protocol assessment in the rest of my presentation today.

So to review, as we've already heard, a little bit more about the validation process, this is for the inpatient VTE among the combined users. We have 614 potential VTE cases. These were all from the inpatient. From that, we had 46 cases with no records available, 25 cases were not abstracted because upon more detailed investigation there was no hospitalization that occurred, despite the fact that this was from the pool initially of inpatients. Seven cases were excluded due to trauma and two cases were excluded with the notion of infant identified. Leaving 534 cases for adjudication, with 405 then definite plus probable cases of VTE or 66% used for the analysis and 129 cases not validated.

So some additional remarks about the endpoint validation process. First, the outpatient VTEs, as you've heard, were validated at only one of the four study sites. And if we then make briefer comments about stroke and the other outcomes, stroke of 241 potential cases, 186 were adjudicated of which 78 were verified or 32% validation with 11 cases having no hospitalization, 11 no endpoint, 19 no records available, and nine trauma, and five infants. For acute myocardial infarction of 92 potential cases, 72 were adjudicated, 60 were validated for a 65% validation rate for analysis, 11 cases had no hospitalization, one had no endpoint and eight records were unavailable.

And you heard this quote before, I present it in a slightly different way, "Because electronic administrative claims data are not collected for investigative purposes, it is vitally important that medical outcomes of interest are validated." Again, from Page 17 of the 2011 draft guidance document.

The data -- a few remarks of the confounders. Key confounders, as we've already heard earlier, may not have always been measured or may have been poorly measured and there also may be missing data for those variables that were obtained, but there was not complete information. Examples -- again, as we've heard earlier, include personal history of VTE, BMI, no distinction between first ever users versus repeat users in the new users group, family history of VTE, and smoking. Some additional remarks regarding the data is that many covariates are required coding for at least two outpatient visits or one hospital code to be included in the database.

I believe many of us are familiar as well with the limited coding that goes in these kinds of databases. As reflected in the third bullet which indicates from the FDA funded study, that the prevalence of most covariates was low, with most occurring in fewer than 1% of women and finally, prevalence of polycystic ovary syndrome or PCOS was 0.02% in the study, while it is estimated that PCOS is present in 5 to 10% of reproductive age women, up to 70% of whom are obese.

Design issues -- the comparator drug group, COMP, was included and did include several contraceptive products with multiple ethinyl estradiol doses. As pointed out earlier, 30% in the 20 microgram dose range, as opposed to the original single dose selection as specified in the FDA protocol. Secondly, preferential prescribing as we again heard earlier, based on age occurred with Yasmin users younger than the COMP or the other subset of the comparator group, LNG. Younger users were presumably as well more likely to be first time ever users. And here we can see that for the age at initiation of the contraceptive, 10 to 24, you can see that Yasmin has a much higher percent than either of the two control groups

In the 25 to 34 age category, it is roughly similar among the three, with reversal among the higher age where the Yasmin had a relatively lower percent of initiation of oral contraceptive compared to either of the two comparator groups. This is actually reflected then in the VTE rate, per 10,000 woman years among all users. As you can see for the two comparator groups, either the levonorgestrel or the combined composite control group, we have the incidence rate unadjusted of either 6.6 or 6.4 per 10,000 woman years, remaining essentially the same for the adjusted incidence rate where it is adjusted for both age and site.

However, to reflect the younger age distribution of the Yasmin users, we see that the unadjusted incidence rate of 7.6 increases to 10.2 for the adjusted incidence rate in this population. Now the effect of age then is reflected in the incidence rate adjusted for age and site. What is not examined and mentioned earlier this morning, is that the effect of first time ever users, and presumably those who are also the younger users, is not reflected then in the new user group, because we are not accounting for the first ever users.

The year of introduction to market of the combined hormonal contraceptive study in the funded study are denoted here, and as you can see, the bottom green line indicates data available for the comparator group, but there are no data available for the first half of the year when the cohort entry began in 2001 for the orange Yasmin group at the top in which the time to market occurred in June 2001. And of course market penetration would have occurred even much later. And for those who do randomize clinical trials, we always like to have subjects being entered so that the patients are fairly similar along the entire spectrum.

We would not design a clinical trial in which for the first half year of that trial, patients would only be included in one treatment group and no patients in the other group. So the goal then for me in doing comparisons is to compare like to like. That is not possible for at least part of the study, which again, cohort entry began in 2001. So some remarks then about analysis. As mentioned earlier, no protocol provided until yesterday for additional review. Second, analytic issues -- compare like to like is preferred and it mimics randomized clinical trials.

What that means is that we would like to be able to compare first time users to first time users, repeat users to repeat users, switchers to switchers, and short-term duration

to short-term duration. The propensity score method allows direct examination of like to like and how well the subjects then are matched to one another. Propensity score has been used increasingly to address confounding and other issues as pointed out in the draft guidance document of the FDA in 2011. Proportional hazards regression is a useful tool, but it is complex and sometimes through that complexity of the modeling process itself, it masks the ability to examine like to like comparisons.

For the analyses that we've seen here, there were no diagnostics presented to support the model, no issues as they relate to goodness of fit. The model building process is a very complex one and so again, in the spirit that this is a first phase of anticipated second phase of the study that I assume that these would be addressed in future work. This is a table that gives the hazard ratio of VTE for the Yasmin versus the overall comparison group by duration of use in the new users. You saw this earlier, so I'll give you a little bit different twist on it.

The duration of use, as seen earlier, was four categories, less than 3 months, 3 to 6 months, 6 to 12 months, and greater than 12 months. So what we see is earliest, an increased risk of 1.93. In the second duration period a non-significant risk of 1.14. Increased again in the third duration of 2.80 and greater than 12 months down again to 1.32. So what we have is an S-shape curve in terms of hazard ratios among these various comparisons according to duration of use. I look at this and even though the risk may decrease over time, if one did have a proportional hazards model appropriate for the data, one might then still expect to see that relative comparison of rates occurring that would, except for random chance, be more or less constant across the four durations noted.

The analysis for ATE, here are some comparisons provided in the data of Yasmin versus the levonorgestrel comparative group. I'm not going to go through all of them, but this is a place where a protocol would be helpful in terms of allowing us to focus of these many multiple comparisons perhaps were prespecified and most pertinent. So as you can see, there are many non-significant comparisons provided and also some significant comparisons provided as well.

Strengths of this first phase of the FDA funded study -- it is a large population size and number of events. It is community based, real world data. Second, it does provide a new user cohort although unable to distinguish truly first time users. It has linked records to state mortality files so that it is able to capture fatalities. It is evaluated in two different U.S. populations. And also, as indicated on Page 41 of the briefing document that acknowledge of the second phase of the study currently under consideration that would include more extensive medical record review, data acquisition of important but missing confounders.

So my overall conclusions of the FDA funded study first phase are as follows. The key endpoint adjudication was incomplete. Confounders were not measured or poorly measured or there's missing data. Again, something common to many of the studies we've seen here, not just to this one. The comparator group included several contraceptive products with multiple ethinyl estradiol doses. Again, 30% had the lower 20 microgram, as opposed to the original single dose selection. As mentioned in the protocol, Yasmin was 30 micrograms only.

Fourth -- no direct confirmation of like to like in the analysis. Further support and work is needed to justify adequacy of the proportional hazards regression model. And

non-overlap of available information among the combined hormonal contraceptive groups in the year 2001.

So what I'd like to do now then is introduce to you Dr. Andrea Lukes and she will provide you a clinician's perspective and she is from the Carolina Women's Research and Wellness Center in Durham, North Carolina.

Andrea Lukes: Good morning. I'm going to give you a clinician's perspective. Before beginning a private practice and a research center three years ago, I had the privilege of being at Duke University for 10 years where I cofounded and served as the Director of Gynecology for the Women's Hemostasis and Thrombosis Center. Before I begin, I'd also like to disclose that I am a paid consultant for today's meeting, but have no financial interest in the outcome.

My outline is here. I'm going to give some general remarks on contraception, and then explain why I think drospirenone-containing pills appeal to my patients and clinicians; give you perspective on the risk of VTE and then a brief summary.

Contraception is one of the leading achievements in women's healthcare within the 20th century. However, as this slide indicates, 49% of all pregnancies are unintended. When you ask those women with unintended pregnancy if they were using a form of contraception, 48% were actually using contraception at the time. So we have a long way to go. If we focus on combined oral contraception, these have been around since the 1960s. So over 50 years of use within the U.S., and most recently the CDC has shown that they are the leading method of contraception.

The risks of VTE in combined oral contraceptive users is significantly influenced by a woman's own risk factors. Further, not all pills are the same. As a provider of healthcare to women, I value choices for my patients. Not all pills are the same and not all women are the same. When I discuss birth control pills with my patients, I go over the different types of birth control pills. First off, a regimen may be different. When pills were first introduced and still the majority of pills have a 21-day hormonal phase, followed by a seven day phase of a placebo pill.

Many of my patients prefer this and are reassured by having a monthly period. There are newer pills that have an introduction of only four placebo days followed by 24 hormonal days and that may lighten the period and give other benefits. I also have many patients that are very comfortable never having a period and we may choose to use an extended regimen and avoid any type of menstrual bleeding. As we heard earlier, the vast majority of pills have only ethinyl estradiol and all of the doses now are below 0.5 milligrams.

I will recommend for women with spotting on the lower dose estrogen that we might increase their dose of estrogen to improve their bleeding pattern. The type of progestins vary much more so than estrogen, given the majority just contain ethinyl estradiol. Here you see other than drospirenone all progestins are derived from 19-nortestosterone. As you hear different generations of progestins, the two on the far left are first generation. In the middle box the norgestrel and levonorgestrel are considered second generation followed by the two below that are third.

In general, the early progestins are considered more androgenic, followed by less androgenic, and then drospirenone is actually antiandrogenic and I'll go over that in more detail. The parent compound of drospirenone as we heard is spironolactone and

this can be used for treatment for acne and lowering high blood pressure. As often as I may start a young woman on a new pill, I also switch women to different pills and I listen to woman complain about the pill they may be using. The most common reasons to stop pills are contained here and include headache, weight gain often due to just fluid retention, breast tenderness, bleeding irregularities, mood changes, and nausea.

I'll highlight drospirenone in terms of mood changes, breast tenderness, and fluid retention and some of the benefits I see with drospirenone. So why drospirenone-containing pills appeal to women? First and foremost, it's contraception and it's effective contraception. In the mid-1990s and 2000 there was data to show that ovarian activity was more inhibited by drospirenone compared to other progestins. This is translated with recent studies to show that real life effectiveness may be better compared to other pills.

I'll go over the two specific properties of drospirenone that give direct clinical benefit to women including the antimineralocorticoid property and antiandrogen. Lastly, the secondary indications are listed here, and these appeal to my patients. Women that have acne may benefit from the antiandrogen property that I'll go over. Premenstrual dysphoric disorder is present in up to 8% of women within the U.S., and profoundly impact a woman's quality of life, and this has been shown in rigorous clinical trials to benefit from Beyaz and Yaz in women desiring contraception.

Folate supplementation is not our focus today, but Beyaz and Safyral contain folate and if you think back about all those pregnancies that were unintended in women on contraception, the benefit with folate supplementation in those cases include prevention of neural tube defect. So the INAS study shown here was published in January of 2011. And if you look on Y-axis, it gives you contraceptive failure rates. And for Yaz, this hovers around 2% versus Yasmin in between 2.5 and 3% and then other birth control pills, close to 3.5%.

So the difference of that 1.5% Yaz versus other, translate just out of the 38,000 and others to 570 women. So if you think of the millions in the U.S. using oral contraceptives, the effective benefit of Yaz translates into a considerable number of women. In terms of the antimineralocorticoid, how does this benefit patients? All estrogens including ethinyl estradiol on the left side give increased antimineralocorticoid activity by increasing aldosterone. This results in fluid retention, increased bloating and increased breast tenderness.

Drospirenone is one progestin that blocks, at a receptor level, the impact of aldosterone. So even though aldosterone may be increased, drospirenone blocks its effect resulting in less fluid retention, reduced bloating and reduced breast tenderness. In terms of antiandrogen effects shown here, drospirenone is again an antiandrogenic, because it blocks the testosterone receptor. This results in less acne, hirsutism, and seborrhea; clinical benefits that appeal to my patients.

So again, why drospirenone containing pills? I've provided information on effective contraception, generally well tolerated. In my experience, the women who begin Yaz or Yasmin are less likely to change their contraceptive and are happy with this pill, and the many secondary indications in addition to contraception.

If I switch now to VTE, it's important for the clinician as we may begin a birth control pill or switch a birth control pill, et cetera, to understand a woman's underlying risk for having a VTE. This slide is certainly not all inclusive, but certain historical

information is needed when we begin a pill. Previous venous thromboembolism, increasing age, prolonged immobility, an inheritable tendency to have a blood clot, and body mass index.

This shows the rates reproductive age women of VTEs. If we were to take 10,000 women and we were to have three cohorts of 10,000 women, the first group on the left who never used a birth control pill and who did not get pregnant, 4.5 of that 10,000 women over a year, would develop a VTE. If you could then take the same 10,000 women and give them a birth control pill, that doubles the risk to approximately 9 per 10,000 over that year.

And then if all 10,000 had gotten pregnant, you see the impact of pregnancy with a four-fold increase with 35 per 10,000 in pregnancy, and up to 80 in the postpartum time frame. As I prepared for today's meeting, I went back to look at the information contained in the package insert and the risk is given as 3 to 9. Also within the package insert there's information highlighting both the Ingenix and the European study and the risks contained, highlighting the prospective nature of those studies and the design looking at the outcome of interest.

The first two studies in the British Medical Journal in 2009 are also reviewed and provide information to the clinician on the limitations of using a database not designed to find this outcome of interest, but to then look back and try and figure out risks, et cetera. If we then look at the more recent studies, Lidegaard, Jick, and FDA and we just -- I just asked and wanted to determine, well what are the risks per 10,000, those are provided here at 9.3, 7.9, and 7.6.

So in conclusion, drospirenone containing pills provide an important and unique role for contraception. The risks of VTEs in COC users are significantly influenced by a women's underlying risk factors. And lastly, the current package insert, in my opinion, adequately reflects the information that I need to counsel my patients on the risk of VTE with drospirenone-containing pills. And I'll return this to Dr. Plouffe.

Leo Plouffe: I'd like to share with you a few final comments and try to bring the discussion together. So we've already talked about Yasmin and Yaz, the differences between the pills, the fact that Safyral and Beyaz also include levomefolate calcium, which is associated, the indication, secondary indication to increase serum folate levels to potentially reduce the risk of neural tube defects. In terms of (inaudible) preparation, Yasmin and Yaz and the content of ethinyl estradiol, both of these clearly fall in so-called low dose COCs. And as ethinyl estradiol is still acknowledges the primary driver for the risk of VTE, both preparations fall in the low dose ethinyl estradiol range.

In terms of the progestin, Dr. Lukes has already shared with you that drospirenone is different than other progestins. It is an analogue of spironolactone, provides antimineralocorticoid activity acknowledged in the label from the launch of Yasmin, to be comparable to 25 micrograms or spironolactone. It is also the only antiandrogenic progestin that is available in the U.S. And from the launch of Yasmin, these factors, these properties of drospirenone, were represented, were acknowledged in the medical literature, in the U.S. medical literature.

The label itself so acknowledges this. So it talks about the comparability to 25 milligrams of spironolactone, provides clear guidance about special patient populations that are contraindicated for Yasmin compared to other COCs, and it also talks about specific medications and specific monitoring protocol to be considered in women being

prescribed Yasmin. So the label also conveyed that information directly about the specific properties.

If we now focus on Yasmin compared to Yaz, and this has been discussed, but just to be very clear, Yaz is a lower dose of ethinyl estradiol. It's a 0.02 milligram or 20 microgram pill, compared to 30 microgram. The dosage of drospirenone is the same in both Yasmin and Yaz, but the dosing regimen is different. So in the case of Yaz, the dosing regimen is of 24 days of active dosing. And this was related to a hypothesis at least that prolonging the days of active dosing could provide better ovulation suppression, better ultimate contraceptive efficacy.

The indications for Yaz include not just the prevention of pregnancy, but also as a secondary indication premenstrual dysphoric disorder and also there's a distinct secondary indication to treatment of moderate acne. Contraindications warning and precautions are consistent across all of these preparations including Beyaz and Safyral.

If we look ultimately at the one dataset that is available, as of now, for the efficacy of the contraceptive efficacy, its comes as a prespecified analysis from the INAS study, the ongoing INAS study that I've discussed, and these are data derived only for the U.S. cohort. And what is being achieved is looking year one, two, and three of follow-up that Yaz has a lower failure rate or hence, a higher contraceptive efficacy compared to Yasmin and compared to other oral contraceptives.

Now we don't have time and we'll be glad to show the data, but we also were able to demonstrate in the INAS study that indeed any 24/4 regimens -- so there are other 24/4 preparations -- do enhance contraceptive efficacy. And if we compare 21/7 Yasmin regimen to other 21/7 pills, there does appear to be an inherent property of drospirenone possibly to its longer half-life that could also enhance contraceptive efficacy. So at the end of the day, all preparations are effective, but it is an area that needs continued exploration.

If we look at the data for PMDD, a key element to understand is the efficacy in PMDD with Yaz is seen in the total score, but both in the emotional symptoms linked to PMDD, as well as the physical symptoms. And ultimately, in the scales that look at impairment, life impairment, there is also a significant improvement with Yaz. So it applies to physical symptoms, emotional symptoms and overall degree of impairment.

Now, there's a lot of discussion today about channeling patterns of use and so on. We did look at the use pattern for Yaz and this study specifically looked during the year 2007 at a large combined healthcare database, at women receiving the first prescription during that calendar year for a specific prescription. So they had no use of COC during the prior six months, none whatsoever, and then they were started on respective pills. What you can appreciate here is that over the year, Yaz has the lowest likelihood of being switched from one pill to the other. So it's not just people starting, but once individuals are started, they tend to stick with that pill compared to other oral contraceptives and that aligns with what Dr. Lukes was relating.

If we look at Yasmin, even though Yaz has now been available for several years, Yasmin continues to be widely prescribed and the data for Yasmin also suggests that refill rates with Yasmin are higher than refill rates with other oral contraceptives, again pointing out that there is a good level of tolerability with the pill. In terms of contraindications warning and precautions, I've already highlighted the contraindications warning and precautions linked to the antimineralocorticoid activity

of drospirenone. The other elements in the label are very similar to other recently approved COCs, with the exception of what's already been discussed by Dr. Lukes of the additional element in the warning and precaution for VTE, discussing specifically the recently published study. So the EURAS and Ingenix and the two 2009 papers.

If we now focus on the risk of VTE with COCs, the label as was already highlighted, conveys that the risk of VTE in COCs users is 3 to 9 per 10,000 woman years. There is also now in recently approved COC, the statement that the risk of VTE is highest during the first your of use. Trying to understand the discrepancies and the challenges in putting all the studies together, we thought it would be helpful to look at all the studies that compared directly Yasmin and levonorgestrel COCs.

And if we look first at the event rate captured in each of these studies, one can appreciate that for levonorgestrel COCs, there is a very, very broad range of event rates. There's almost a three-fold difference between the lowest estimate which is the 3.2, all the way to the highest estimate at 9.2. So this is very inconsistent risk estimate for the same oral contraceptive, albeit across studies. If we compare Yasmin, we find that across studies, the point estimate is much tighter and the variability is about 1.4 fold, which is well within the acknowledge range of observational studies.

So we think it's important to keep this in mind when we're comparing studies for relative risk or hazard ratios and really look at where's the difference? Is it in the estimates for drospirenone Yasmin or is the difference in the comparator preparation? So at the end of the day, we're very much aligned with our colleagues from the FDA that when we look across these studies, it is puzzling to understand what the differences. Why are there such wide differences in the results being seen?

We think a key element that's already been discussed this morning, is the challenge in establishing like to like cohort. The challenge in assembling populations that are truly similar that can be well compared. We do think that the two post-approval commitment studies did focus on that upfront, and this was through extensive discussion respectively with the FDA and the EMA and both of these studies show a risk being similar for Yasmin to other COCs.

Now, Bayer is deeply committed to this area of research, has been for many years and continues to be. We welcome the dialogue today. We welcome the thought of the FDA to do a follow-on study, the planned second step of their current undertaking. We also want to point out that we have the ongoing INAS OC study. We have the INAS score study which is relevant to another oral contraceptive that Bayer introduced in the marketplace, Nataza. And we have another international active surveillance study, the INAS focus study, looking at folate preparations.

So we welcome the outcome of today's discussion and look forward to ongoing discussions with the FDA and the EMA to see if we can make even better use of these studies, what adjustments we can make to make sure we ultimately get to a clear answer on this topic. In the meantime, the best available data suggests that the DRSP OCs do expand the range of available options and indication. The risk of VTE is similar based on the Ingenix and EURAS/LASS trial. The risk of ATE is similar based on the LASS data, and the interim data from the INAS study provides data that Yaz is also similar for its risk of VTE.

Ultimately, we believe that the DRSP OCs are an important treatment for prevention of pregnancy and they offer a favorable benefit risk when they're used according to the

U.S. label. Thank you. And I'd like to make the panel also aware that we've got a number of external consultants should you have any specific questions. So we'll be glad to make them available.

Julia Johnson: Thank you. I'd like to thank the sponsors for their presentations. Now is our opportunity to direct questions at the sponsors. These questions will for this 15-minute period be directed to the sponsors. We will save any questions that are directed back to the FDA for our afternoon session. And again, please raise your hand and Ms. Bhatt will record who has questions and we will move ahead with those questions in the time allowed. So first, Dr. Suarez- Almazor?

Maria Suarez-Almazor: Yes. My question is about benefits. In order to make an informed decision about risk benefit we need to know not just the risk, but also the benefit and there's been very little discussion. There's been just one study that has been shown which is based on life table analyses on contraception and I was wondering if there is any clinical trial data that -- or any other additional data that looks at efficacy that the sponsors or the FDA would like to share with us.

Leo Plouffe: I think that Dr. Willett discussed the primary data obviously come from the pivotal registration trials and those are generally presented in terms of contraceptive efficacy in terms of Perl Index. So as Dr. Willett commented already today, the contraceptive efficacy is well-established. The Perl Index that were generated for both Yasmin and Yasmin are in the upper end of the efficacy range, but these are not comparative trials. Most oral contraceptive trials as you know are single arm trials. So the elements there are aligned with finding a high level of efficacy with these pills.

The INAS study was the first actually large scale trial that we're aware of, that was undertaken comparing contraceptive efficacy. And I say, shared the data with you, this study is ongoing. We're looking for similar in Europe. In Europe, generally speaking, contraceptive efficacy rates in trials are greater, are higher than the U.S. Nobody knows why that is. But we're obviously continuing to monitor that.

Julia Johnson: Dr. Raymond:

Elizabeth Raymond: Thanks. I have actually two questions. The first question is about the Seeger study. Can you give us any insight into what pills the comparison group were taking?

Leo Plouffe: Yes. So the comparator in the Seeger study that I otherwise referred as the Ingenix study, were all the pills in use at the time in the U.S.; so all available oral contraceptives. So that includes norgestimate, norethindrone, levonorgestrel, desogestrel and others. So that's the range of pills that were in use. That's very important -- these are the number of individuals that started these pills. It's important to remember any time we look at data from the Ingenix study that it's a propensity score matching, so we can't just do direct comparison here. We'd have to go back to recreate the cohort, but that's ultimately all the other pills that were used.

Elizabeth Raymond: Okay. Thanks. And my second question is about something that was mentioned just sort of briefly, when I read the papers by Parkin and Jick, I thought it was sort of peculiar that they included only idiopathic VTE cases. And they did this, as I understood it, because they thought that this approach would -- that an association between drospirenone containing pills and VTE would be more apparent if they used this approach. I don't know if that's necessarily true, but if it is following that logic, it seems like those studies would have been explicitly designed to overestimate the risk

or the association. And I'm wondering if you can comment on that? Did I misunderstand that? Is that --

Leo Plouffe: So from our reading of Dr. Jick's work and some of the discussion, there is the notion that sometimes focusing on only idiopathic cases could unmask an effect. One of the challenges is looking at the notion of idiopathic, is that the definitions vary from one study to another. And because of that, it becomes a very difficult area to look at. So for example, if we look at Dr. Jick's studies which are represented as the Jick et al 2006, 2010, 2011, and she was also one of the investigators in the GPRD study. You can appreciate that the criteria to define idiopathic cases varied from one study to the other. So that makes it very difficult to really know what idiopathic exactly is.

I mentioned earlier that in the last study, we did do a subset analysis for idiopathic cases and you've got there the definition that was used by Dr. Dinger to look at the idiopathic subset and we'll be glad to share these data if there is a desire to see that analysis. But ultimately, the concept is that there is a lot of variability in the definition itself. Now we still prefer whatever is done, we still think the important thing is upfront, presenting all of the information, presenting all of the data.

And this is one of the unfortunate elements we think in both the PharMetrics study and the GPRD is we're not given access to all the data. So I think it would be much easier to draw our own judgments if we were able to look at the entire dataset and then look at the impact of idiopathic only cases. But at this point, that's not possible. In the PharMetrics study, we know that only 39% of cases were idiopathic. In the case of GPRD, that was not revealed.

Julia Johnson: I'm going to warn the committee that we will not get to all questions before lunchtime. We will extend this portion for another five minutes to allow some questions to be answered, but some will be saved for the afternoon. Dr. Wolfe?

Sid Wolfe: This is for Dr. Lukes. You're absolutely right; it is very important to have a clinician's perspective and also equally or more important the perspective of women and patients. In the wake of extraordinary decreases in the prescribing of Yaz and Yasmin starting after the British Medical Journal articles and even more so after the label change, just a question for you. In your clinic, or in your practice in your clinic, have you also seen a decrease in the use of these two drugs relative to other contraceptives? And if you have, why do you think it occurred? And if you haven't, why do you think it didn't occur?

Andrea Lukes: I have seen a decrease and as a clinician I have had women over the last few years come to me concerned that they've seen advertisements that Yaz or Yasmin can cause more blood clots. So I've tried to stay abreast of the information and in my judgment I do not think that there is an increased risk. However, as a clinician, when I am seeing one patient, if her anxiety is going to allayed by switching her pill, then I switch her pill. So even as a clinician, I've taken some women off -- not based on evidence, but on a personal basis.

Sid Wolfe: The follow-up is do you then not tell them that you think that there is an increased risk? I mean how do -- you're handling that question. I mean you're saying, as you should, you respect their wish to switch to something else. But since you're the clinician, do you acknowledge or do you say to the woman, you've read that there's an increased risk. I don't think there is. How do you handle that? That's really my question?

Andrea Lukes: Well, it's changed since the studies have been emerging. Initially the package insert changed, which was in in 2010. I thought very insightful and pointed out the limitations of the two studies in the British Medical Journal. I'm very upfront and I -- I think a lot of the commercials seem to have been more driven by litigation or seeking cases from my understanding. So I reassure patients about that. As more studies came out more recently, I referred to some of the FDA -- I knew the FDA had a study and I just have an open dialogue. And personally, I still was not at all (inaudible) it increased the chance of having a blood clot. But I, you know, in some ways it's a good raising of awareness; that it reminds all clinicians that birth control pills increase a woman's chance of a blood clot.

Julia Johnson: Thank you. Dr. Hernandez-Diaz?

Sonia Hernandez-Diaz: I agree many of the limitations mentioned in the presentation, but I think that the point is can these limitations explain the differences in results. And one of my questions was about confounding, so I'm going to focus on that one for now. Regarding the potential impact of confounding, in the different findings that we are seeing, perhaps we can learn more from the studies presented. For example, in the experience of the EURAS study where there were confounders available that might not have been available for the FDA studies, can you remind us of the impact of adjusting for the confounders that were available in EURAS because of the access to more information?

How did they change? And perhaps if you could highlight the ones that we really need to have in our studies. And same thing with the propensity score analyses, if you can identify the kind of factors that were crucial in the estimating of the propensity scores and that we should have in other studies.

Leo Plouffe: So I'll start first with the EURAS study. So one of the elements in the EURAS, we did at the request of the FDA, look at various risk factors and the contribution of various risk factors. But the group at Center for Epidemiology had already been looking at these. So, for example, they did generate data about the interactions between age and BMI. And so there is a factor not just about the age itself, but age and BMI are factors that are interrelated.

So if we look from the EURAS study specifically at the impact of individual factors, you can appreciate these are the hazard ratio, the adjustment and then the adjudicated hazard ratio for these. Age is an important factor, BMI, duration of use, and history of VTE. And then you've got multiple factors and the multiple factor analysis coming in. At the end of the day and we've had discussions with Dr. Dinger on this, one key element though is all of these, the magnitude of the effect is computed within a cohort that was overall very similar at baseline.

So it's very difficult to extrapolate these data or this information, if you're not starting off with relatively similar cohorts. And the FDA very appropriately pointed out, the EURAS cohort, it's an observational study. It's a population based study. But they were women willing to participate in the study and they were predominantly seeking contraception as a primary driver. So from that perspective, these data we think are helpful to start establishing a roadmap, but we think there needs to be a lot more discussion about the relative contribution of these factors.

Julia Johnson: We're going to allow for two more questions and then we'll take a break and bring these back. Dr. Burke? Okay. Ms. Aronson?

Diane Aronson: I want to follow-up on a question on prescription trends, and just wondering about the enhanced counseling that may have taken place. Do you have any analysis about whether the prescriptions were provided from primary care physicians or OB/GYNs?

Leo Plouffe: The information we have is the predominant prescriptions for Yaz and Yasmin come from the OB/GYN community. There's obviously a very important role played by primary care providers, both physicians, nurse practitioners, NPAs, but the predominant prescriptions come directly from OB/GYNs.

Julia Johnson: And one more question. Dr. Tepper?

Naomi Tepper: I actually had two I think fairly quick questions. One was just to go back to the issue of, I think in Ingenix study of the comparison group and whether it's possible there were progestins in the control group that might have increased the risk for VTE in the comparison group?

Leo Plouffe: So you may be referring, actually in the briefing document we said the FDA had requested that breakdown. And so we have that information of the breakdown of the progestin and the woman years of use of the different progestins around this. I think a key element around these data -- we need the most recent analysis with duration of use. You'll see the data in a second, but a key element of looking at the data like this is these are purely the raw data extracted from the database. They have not gone through a repeat propensity score.

While my colleagues are finding the slide, basically about, there were less 10% of women using desogestrel, which I think is one of the progestins that have been highlighted as a potential high-risk progestin. So it's really a small contribution to the cohort. If we look at the VTE event rates that can be calculated, the raw event rates for these, for Yasmin the event rate as presented -- so the Yasmin data are exactly what you see in the primary paper which is 13 per 10,000 woman years. In the other COC, it's exactly what's represented in the paper, 14.

Please do remember this, the mean follow-up here is 7.6 months, so it's primarily a first year cohort. If we look at the incidence -- the event rates for the others, levo was at 12 with confidence interval of 4 to 26, norethindrone was at 19, at 10 to 31, norgestimate at 10, desogestrel was at 16. And then you can appreciate the relative size of the different cohorts for the other OCs. So hopefully that answers -- and again, to really get to the bottom of that question, we'd have to recreate the entire cohort and do propensity score.

Naomi Tepper: I just had a question for Dr. Makuch. I was wondering if you could just explain again the issue of adjusting for age, the implications of adjusting for age and that changed the incidence rate in the Yasmin group more than in the comparator groups.

Robert Makuch: I think it did so because the age for the Yasmin users is so much younger. And so when you do the adjustment for age and site, essentially it is then using the comparator group as the basis for normalizing that rate. And since it is a younger group to make it comparable then increase as a result of that age distribution imbalance that occurred in the previous slide to this one.

In slide 87, I think the usage by the three age categories, 10 to 24, 25 to 34, and 34 to 55, you can see how the distribution of percentage of usage changes as a function of those various age categories with the Yasmin being predominantly used in the earlier

age group and the comparator groups being used primarily in the latter age group. And as a result of that, it leads to that change after adjustment for age and site in the adjudicated incidence rate.

Naomi Tepper: So if the investigators adjusted for age, then would their final analyses then be accurate? Then they have controlled for age, so would you consider that to be appropriate?

Robert Makuch: Let me try to give you a brief answer to a really complex question. One, I haven't seen the data. And so the best I can this is being more or less a collegial discussion. But secondly, so unless the model really has a very good fit to the data, we've heard some discussion this morning about interaction terms of age by group interactions. We've heard about site by group interactions. That to me starts to raise issues about simple modeling that whether or not then simple inclusion of an age only factor in the model, whether or not it really then adequately compensates? Perhaps for the more complex picture, that seems to be evident and was mentioned this morning.

Julia Johnson: Thank you. I would again like to thank the committee for their patience in allowing us to run a bit over. We will meet again in 50 minutes at exactly 1:00. We will now break for lunch. We will convene in this room. Please take any personal belongings with you that you may want at this time. The ballroom is secured by FDA staff during this break. Panel members please remember that there is no discussion of the meeting during lunch, amongst yourselves or any members of the audience. Thank you. See you at 1:00.

(Break)

Julia Johnson: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of each individual's presentation at the beginning of a written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its products, and if known, it's direct competitors. Of course this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at today's meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their considerations of the issues before them today.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way such that every participant is listened to carefully and treated with respect, courtesy and dignity. Therefore, please speak only when recognized by the Chair and I think you for your cooperation. Note that each speaker will have three minutes, and at the conclusion those three minutes, just so you will that the microphone will turn and you will asked to have a seat.

There is an exception of one speaker who had been given additional time due to the donation of time from other speakers who had previously registered. So now we will begin with our open public hearing with speaker number one.

Diana Zuckerman: Thank you very much. I'm Dr. Diana Zuckerman. I'm President of the National Research Center for Women and Families. Our center does research looking at the safety and effectiveness of various medical treatments. We're independent, nonprofit. We do not accept funding from pharmaceutical companies or companies that make products that we'd be evaluating, so I have no conflicts of interest.

My perspective is a someone, I'm trained in epidemiology at Yale Medical School. I served on the faculty at Vassar and Yale, conducted research at Harvard and in the course of that, some of the time I was teaching research methodology courses. I'm also on the board of the Reagan Udall Foundation and the Alliance for a Stronger FDA. These are two nonprofits that are dedicated to improving resources for the FDA and I'm also a fellow at the University of Pennsylvania Center for Bioethics. So I just say that at that's my perspective coming from that background.

I'm going to talk a little bit about the research methods. Of course you've heard and know that are conflicting findings in the different studies. I'm going to talk a little bit, particularly about the FDA study, but first I want to say something that I think is obvious. We all know that there's plenty of research showing that funding sources influence research findings and there have been numerous articles in JAMA and many other medical journals showing the impact of funding and how that affects the fact that studies that are funded by a particular entity tend to show that their product is safer and more effective than other studies show.

And that doesn't mean that the researchers are intentionally misleading or misrepresenting the data. Sometimes it's absolutely not conscious. People believe in the products that they're working on and studying and they tend to accept the good findings and discount the negative findings. But sometimes, of course, research methodology is manipulated in order to maximize the likelihood that findings will be positive. And I just want to say, and although I think the panel has not been given access to the Kessler (ph) report that was recently made available, it did have some very specific examples where Bayer was misleading and misrepresenting VTE findings.

The FDA study has 800,000 women, which is a remarkable sample size and its very important and they've separately analyzed new users and other users and that's also very important -- a very good and important strength and might partly explain some of the different findings. I also want to talk a little bit about selection bias. I found some of the questions about selection bias really surprising. We know that Yaz and Yasmin are brand name drugs that cost more; cost more than many generic birth control pills. So as a result of that, the women taking them would tend to be more affluent.

And the research is very clear on this, that more affluent women tend to have lower BMIs and be less likely to smoke. So if there's a bias in selection bias, even at Kaiser Permanente where perhaps the drug costs are mostly paid, there's still a copay and the copay is higher for brand names than it is for generics. So one would expect that if there's a selection bias, the women getting Yaz or Yasmin as the case in most these studies, would tend to be more affluent, lower BMI, less likely to smoke. So it may be very different in Europe, but in the United States, which is what we're concerned about

todays, there's every reason to think that if there's a bias, it would have been that the women taking Yaz would have been less likely to have VTEs, not more.

Likewise, the fact that the Danish study showed that there were inaccuracies in VTE diagnosis. I don't think that's relevant to the FDA's study, which was in the United States. And also just want to mention, if somebody's having something might be a VTE, if it isn't, what is it, and that doesn't mean it's nothing or not important. So that's about the confounding variables. In looking at the studies it seemed to me clear that you could not make the case that the benefits outweigh the risks for birth control pills with DRSP. And so, in my opinion, absolutely, these drugs should not be on the market because there are safer alternatives.

And the benefits for acne and for PMDD are mostly compared to placebo, not to other drugs and also you have to look very carefully at how those terms were defined. It's not all acne. It's not all PMDD symptoms, so you really have to look carefully at these and you'll see that the benefits are not enormous and not proven compared to other birth control pills. The labels -- just wanted to show, these are the labels just for Yaz and Yasmin. They're huge. They're really too big for people to read, and I just want to say that doctors have been influenced by advertising just the way patients have been. You're going to hear more about that today. Patients who were not adequately warned and doctors who did not understand the risks even when patients were harmed. Thank you.

Julia Johnson: Will the next speaker come to the podium?

Dana Casciotti: Hello. My name is Dr. Dana Casciotti. I have a Ph.D. in public health from Johns Hopkins. I'm speaking today on behalf of the Patient, Consumer, and Public Health Coalition which is an informal coalition of several dozen nonprofit organizations. These organizations represent millions of patients, consumers, scientists, ethicists, and public health researchers. We do not have conflicts of interest.

While all studies have strengths and limitations, most of research reviewed for today's meeting indicates an increased risk for women taking DRSP containing birth control pills. I would like to briefly focus on the strengths of the FDA study which was an enormous cohort study including over 800,000 U.S. females with over 800,000 person years of exposure to contraceptives.

Women were excluded from this study due to serious or life-threatening illness, history of VTE or CVD, or pregnancy, thus excluding some of the women at highest risk for blood clots. All hospitalized outcomes were validated. The FDA study contained two exposure cohorts, current users of DRSP and new users. It also included two comparison groups including women taking four different types of progestins with low estrogen levels.

Another important strength was the separate analysis of women in different age groups and controlling for age within each age group. This study found that DRSP increased the risk of VTE by 70 to 80% compared to the low dose estrogen pills in both the all user and new user groups and was especially prevalent among younger women. New DRSP users also experienced doubling in risk of ATE, especially among women 35 and older. FDA study results are also consistent with four of the seven epidemiological studies reviewed by the FDA in the committee's background document. Thus, five studies demonstrate an increased risk of DRSP containing pills. The only studies that

showed no increase in blood clots were conducted by researchers with very close ties to the companies that developed these drugs.

Those studies did not separately analyze different age groups and did not separately analyze new users and that could explain different results. One of those studies does not specify the comparison contraceptives in the non-DRSP group and the studies did not exclude women with higher risk of blood clots, such as those with cardiovascular disease. One of FDA's questions is about risks and benefits. I hope you'll agree that because there are safer alternative oral contraceptives, the benefits of DRSP containing pills do not outweigh the risks.

Finally, regarding current labels, they do not adequately provide useful, easy to read information about risks. Few doctors or patients would read the labels because they are so long and contain so much information that would not be of interest. Unfortunately, even the best labels with large, clearly stated black box warnings could not be effective as long as these contraceptives are widely advertised in ways that bury risk information and persuade women if they want to be attractive and happy, they should take Yaz. Thank you.

Julia Johnson: Thank you. Will the next speaker come to the podium?

Professor Fodor: Good afternoon. My name is Professor Fodor (ph). I am a Belgian obstetrician and gynecologist and although I was performing the pivotal studies concerning the Yasmin in Europe, I am not affiliate with Bayer and I have no conflict of interest concerning this presentation. I just would want to draw to the attention of the panel that estetrol so recently described new estrogens which is from human fatal origins and estetrol and estrogen in most issues, but except in the breast where it is an antiestrogen and it has a neutral impact on the liver.

We have combined estetrol as a new estrogen with drospirenone at the dosage of 3 milligrams and various doses of estetrol were confronted in young women for three cycles of treatment and this was compared with Yasmin. And it is shown on the upper panel that the Yasmin users as shown in black, showed as traditionally observed, a huge increase in the SHBG or angiotensinogen plasma level or in the (inaudible) plasma level. This is due to the impact of ethinyl estradiol on the liver centers is (inaudible) estrogen dependent liver protein.

When we compared on more than 20 different coagulation and (inaudible) markers, the impact of estetrol in blue and red, or each of Yaz in black, we could see that as anticipated Yaz containing ethinyl estradiol would have quite a significant impact on the several coagulation markers like antithrombin, protein S, TFPI, protein C, and on the fibrinogen or the APC resistance. For example, the APC resistance as shown in the black panel in Yaz users was increased more than 200% while it was not modified when estetrol was combined with drospirenone instead of ethinyl estradiol.

So for example, the fibrinogen degradation product, or the F1 and F2 fragments of fibrin, are also completely different in Yasmin users in comparison to the estetrol containing molecules. In conclusion, I want to just stress that the association of ethinyl estradiol (inaudible) drospirenone may convey an increased risk of DVT. However, in association with (inaudible) of drospirenone, estetrol at varying doses up to 20 milligrams, who much less changes in the coagulation of (inaudible) markers. This just indicate --

Julia Johnson: Thank you. Will the next speaker come to the podium please?

Diane Hammonds: My name is Diane Hammonds (ph), a retired fifth grade teacher. I am speaking for my daughter, Ann, today since she is dead. Yaz silenced her death. We are here to honor her life by preventing future drospirenone deaths. At midnight, November 6th, 2009, Annie and I were laughing at Jay Leno. She took her last breath as she slept that night. The police report indicated sudden death. Ann's death shocked everyone who knew her. She was young, healthy, athletic, a runner, a physical trainer, and a new lawyer. She ate healthy foods, was a non-smoker and had a low BMI. Her lifestyle did not contribute to her death.

The medical examiner thoroughly examined and found only a microscopic heart attack. No other heart abnormalities or signs of cardiovascular disease were found. She was dehydrated. Ann was prescribed Yaz eight months earlier, not for birth control, but for irregular periods, not a life-threatening condition. Ann's physical ailments then started, extraordinary weight gain, hair loss, headaches, insomnia. You can see some of those changes in these photos.

Later lab work showed rising potassium levels. Drospirenone was (inaudible) to dehydrate and pills containing it are the only ones whose warnings state that they may fatally increase potassium levels. DRSP is the only OC that changes blood chemistry. Despite Ann's numerous visits to her GYN primary care physician and an endocrinologist, none suspected Yaz. Yet after Ann's death and finding this partially used packet, it took her sister only minutes of research to realize what had been attacking our Annie.

Tragically, Ann finally suspected Yaz two weeks before her death when she got her last refill. She never got the full package insert, but when she saw the watered down pharmacy warning, she called her GYN to say she was having with problems with Yaz. She was not advised to stop the pill. Ann died before she saw her doctor. We now know our daughter's death is not a rare occurrence with Yaz. Hundreds of deaths and thousands of blood clots attributed to DRSP have been reported to the FDA. Many drospirenone deaths and serious injuries are not reported.

Doctors assume that all FDA approved BCs are safe and medical examiners are not permitted to list FDA approved medications in our group. Talking with anyone who would listen after Ann's death, most women or someone they know has had a blood clot problem with drospirenone. It is not rare. That shocks us. Ann died because she trusted the U.S. medical system. She died because she took her FDA approved medication as prescribed. DRSP killed our healthy athletic daughter. She experienced many Yaz side effects and then the ultimate one, sudden death. Her killing, not even officially recognized as a killing is incomprehensible to me, Ann's mother. She should have been at our Thanksgiving table this year and next year and the next.

Ann's and our experience with doctors shows that merely changing the label or fine print warnings is not enough to protect young women from unnecessary death. Safer birth control pills are available and there's no reason to keep a dangerous one on the market. Please make sure that no other family has to go through what we are because of unsafe, widely advertised and widely used birth control pills with blatantly misrepresented risks.

Julia Johnson: Thank you. Next speaker?

Unidentified Participant: We have no financial interests in the outcome of this, other than my wife having donated her salary this year to advocacy efforts to get Yaz off the market. My wife and I, Annie's mother and father, have spent our adult lives defending and serving our country. We are here to provide some clarity so you know what should be done and to ask you to do your duty to our country's citizens. Our daughter died from Yaz. Her death was totally preventable and that is true for possibly thousands of women who also died or will, from Yaz.

Study after study, including the FDA study, have shown for years that DRSP kills and seriously harms significantly more women than other birth control. Studies funded or conducted by Bayer all seem to indicate that DRSP is no worse. Obviously, it is not in Bayer's interest to be impartial. There are many ways studies and analyses can be adjusted to produce favorable results. As we've seen today, money can buy a lot of smoke generators.

Increasing warnings on the label won't work. Even when the FDA required Bayer to remove unsupported claims and increase its warnings in the direct to consumer adds, Bayer's TV commercials targeting young women, continued to downplay the risks and use distracting noises and graphics so that the warnings of blood clots would not be noticed or taken seriously. Dr. Lukes was paid to review the package insert, reinforcing the truth that doctors don't memorize the warnings on the drugs they prescribe.

Drug industry efforts to influence the medical profession are well documented. So educating the doctors who are also being influenced by Bayer's ads, promotional activities and regular drug rep visits is swimming against a strong current. The black box warning treats DRSP just like other birth control pills, but it is not. Bayer's FDA approved label warns of potentially lethal elevated potassium levels from Yaz, a risk unique among birth control pills. All birth control pills sometimes cause blood clots, but the tragic truth is that DRSP brings significantly greater risk and no benefits over less dangerous oral contraceptives.

Bayer's bottom line is the only place there will be a positive outcome from keeping Yaz on the market. Even with only two years left on its exclusive right, Bayer stands to lose billions of dollars if Yaz is taken off the market and billions more if it loses the new approval for BS (ph). Bayer is exerting enormous pressure to avoid that financial outcome. We know that the FDA advisory committees don't like to recommend that a medication be taken off the market. They'd like a compromise such as stronger warnings. It didn't work in 2003, 2008 or 2010 and it won't work now. Even if warnings were more effective, if DRSP pills remain on the market, the truth is more women will die than if it is removed. Please help save those lives.

Over a thousand U.S. women have been suffering blood clots from DRSP every year. Some of them die. But many of those women, over 400 of them, would not if they used another birth control pill. These are people, not numbers. When a colleague came to support me in my grief, I learned his 20-year-old daughter was suffering from DVT symptoms that her doctors found inexplicable. I told him that she should switch to another birth control pill is she was taking Yaz. She was. She switched. She quickly regained her health. I may have saved a life. Think of how many women's lives --

Julia Johnson: Now to speaker number six, would you please come to the podium?

Shayla Beyers: Good afternoon. My name is Shayla Beyers (ph) and today I stand before you as one very, very lucky woman, a survivor with the opportunity to speak for the rest. I have been an athlete for as long as I can remember. In fact, only six years ago, I was a starting varsity field hockey player for Dartmouth College. So you can imagine my shock when at the age of 25, just a few short years after graduation, I found myself in a hospital room hooked up to two machines, hoping to live through bilateral pulmonary embolisms and a massive DVT in my upper right shoulder.

I had been on oral contraceptives without any problems for years, but was convinced by a doctor to try the new product on the market, Yaz. I was exactly the demographic they were looking for, non-smoker, athlete, no history of any major medical issues, normal BMI. I was not told then nor was I told when I was unknowingly switched from Yaz to generic Yaz, that these pills carried a higher risk. If I had been, I would not have used a pill with more risk.

The complications I faced as a result of this experience included, but were not limited to liver and kidney failure, lung collapse, rib removal and a scalenectomy. I attribute it to Yaz, because I had been on hormonal birth control before and my body did not react this way. I believe it was Yaz, because all of the independent studies conclude that Yaz carries a higher risk of blood clots than any other birth control pills. The only studies that don't, in fact, have significant financial ties to Bayer Schering. Hmm, isn't that convenient?

You were given this brief right here, to read and prepare for this meeting. If I had been your daughter, would you have devoured it page for page, like my father did. These ZEG studies are the only ones that supposedly prove that these drugs are as safe as other pills, but ZEG employees are former Bayer Schering employees and there are other connections that financially bind the interests of these two parties. The ZEG studies cannot be trusted and all other studies show an increased risk.

If you file a Foyer (ph) request, you just might find that Dr. Lidegaard specifically wrote to the FDA to request the opportunity to speak at his own expense here today and he was denied. Further, the FDA never even bothered to reach to Dr. Jick to obtain her opinion. I wonder what she would have said. Is this adding for you the way it is for me? I want to thank the FDA for pointing out the inherent bias of advisory committee members that maintain ties with Bayer Schering. Would those who maintain those ties please raise their hands? Feeling shy?

I ask that you remove yourself from the vote entirely. To me, this isn't about getting even, nor is it about banning all birth control. It's about acknowledging that there is a highly destructive birth control on the market and recalling it. I ask you to do this above ego and above bias, because it's the right thing to do.

Julia Johnson: Thank you. Now, number seven.

Cindy Rippy: My name is Cindy Rippy (ph). Next to me is my daughter, Veronica. Veronica's twin sister, Elizabeth, is on the screen. Elizabeth was lovely and gracious and she made a difference in the world around her. On Christmas Eve, three years ago, in a bathroom of our home, I gave Elizabeth CPR trying to save her life. Elizabeth died in the hospital emergency room. I want to share with you our last conversation.

Elizabeth turned to me and said, "I love you, Mom" and I said, "I love you too, Sweetie." She asked, "Am I dying, Mom." I answered, "I don't know, Sweetie. You're

awful sick and they don't know what's wrong with you." She said, "I don't want to die, Mom." Elizabeth died of pulmonary embolisms in both lungs. She was only 20 years old. She had switched to Yasmin two months earlier.

She had taken generic Ortho Tri-Cyclen for over one year without any problems. I hope you never experience the devastating loss of a child. The deaths of other women can be prevented by this committee's work. The issue here is warning our daughters, our sisters, our granddaughters, that these pills are more dangerous. My daughter was a very smart, young woman. If Elizabeth had been clearly warned that Yasmin had more risk, maybe twice as much risk than other pills, she never would have switched to Yasmin, never, and she would be alive today.

Bayer, Dr. Dinger, I hold you accountable. Why was she not told? She had a right to know clear and accurate, true information. I am here to say today that I do not want other daughters, other women to die because the information is unclear. It would be despicable enough, Dr. Dinger, if it was only 10% higher, 50%. Seventy-seven percent or greater? Europe, where you live, Dr. Dinger, warns of a higher risk. Australia warns, Canada warns, England warns. England tells their daughters that the totality of available evidence now clearly shows that the risk of venous thromboembolism for Yasmin is higher. Higher. Not the same, not questionable, not unclear -- higher.

These are our children. They are not your customers. They are not numbers in a study and they are not numbers on a balance sheet. We did not raise them to make money for Bayer. And we did not raise them because a drug company has a drug that shouldn't be on the market. To the FDA, remember your mission. To protect the public and ensure the safety of products.

Veronica Rippy: Elizabeth was my twin sister. My only sibling. My everything. Young women in America do not need more dangerous pills on the market with confusing information. Get rid of it. Be smart and do the right thing.

Julia Johnson: Thank you. Number eight, can you please come to the podium?

Cindy Pearson: I'm Cindy Pearson, Executive Director of National Women's Health Network. Familiar to many of you, because we've testified before the advisory committee on reproductive health drugs since it first opened its doors to the public. And you know, from my many disclosures that we're independent. We take no financial support from any part of industry. What you may not know, is that we were founded 40 years ago by women who had the nerve to stand up. The only place the doors were open, which was Congress, to stand up in the middle of a hearing about oral contraceptives and ask that their questions be answered.

I didn't come expecting to talk about them today, but being so moved by hearing women stand up today and speak about their experience, I think it's important to talk about the arc of history. Forty years ago today, or close to today, women were celebrating the support of their government for their contraceptive choices, unlike yesterday and today when we're frustrated. But those women were, at the same time, upset that what was in many ways and enormous advance, was also dangerous and dangerous in ways that were not revealed to them and possibly did not need to be as dangerous as possible.

When women spoke up, Congress listened, FDA listened, the manufacturers listened and the arc of history took us to a time with safer products. The high-risks of blood

clots and other problems caused by those high dose pills have come down. It appears as clear as epidemiological evidence can make it be clear, that drospirenone-containing pills are taking the arc of history and progress backwards. They are more dangerous than earlier combinations of pills, and they have no well-established unique benefit. We heard some interesting speculative benefits, but well-established based on data.

So you, the committee, have been asked by the FDA to answer some questions about data. We think those questions are pretty well answered and where women need you to turn your attention is what should the FDA do? You've heard very eloquently that information in labels doesn't get all the way to patients and even a little bit earlier that it doesn't get all the way into the habits of clinicians. What we need you to do is advise the FDA to use the regulatory tools at its disposal and to take these more dangerous and no more beneficial products off the market and get back to the arc of history and progress that protects women while supporting their contraceptive choices. Thank you.

Julia Johnson: Thank you. Number nine, if you'd please come to the podium?

Vanessa Cullins: Good afternoon. I'm Vanessa Cullins. I'm Vice President for External Medical Affairs, Planned Parenthood Federation of America. I have no conflict of interest as it relates to Bayer Pharmaceutical Company or the FDA. Planned Parenthood Federation of America and I believe that there should be a broad array of safe, effective, contraceptive methods available to both women in this country and worldwide.

Thank you for allowing me to make comments on behalf of Planned Parenthood Federation of America. At Planned Parenthood, we serve over three million women contraceptors each year. Firstly, we want to commend the FDA for making a science based decision around Plan B. One step being over-the-counter for all childbearing potential women who need it. It is just extremely unfortunate that the Secretary overruled this science based decision. We ask that decisions around drospirenone and Evra be based upon science.

The two-fold increase in venous thromboembolism that is now being seen in some observational studies for drospirenone is also seen in observational studies around desogestrel and also Evra. The two-fold increase in risk is deemed an acceptable risk and has been deemed an acceptable risk in the past. All of these products should remain on the market without FDA imposed restriction because the two-fold risk is still extremely rare and it is dwarfed by the VTE risk that is seen in pregnancy and during the postpartum period.

Planned Parenthood recommends that providers and women be made aware of the risks so that informed contraceptive decision-making can occur. The issue you are deliberating upon both today and tomorrow is the two-fold risk of VTE that is seen in some contraceptive products when compared with products that contain older levonorgestrel progestin. Based upon science, all such products should be treated the same and should remain available to all women in this country. Thank you.

Julia Johnson: Thank you. Speaker number 10, it will take us just a moment to get your video up, but if you would come to the podium. Thank you for your patience. Thank you very much.

Joan Cummins: My name is Joan Cummins (ph). My daughter, Michelle, was an amazing young woman. Vivacious, beautiful, accomplished. She was looked up by her peers and cherished by her family. Michelle was extremely intelligent and was an exceptional

student. At 18, she was just starting her freshman year at Elon University in North Carolina when she collapsed on her way to one of her morning classes on a day I will never forget, September 24th, 2010. She was rushed to the hospital by paramedics but died from cardiac arrest from a pulmonary embolism.

My daughter was on Yaz. One day, she was a healthy 18-year-old, full of life with a promising future ahead of her and the next day, she was gone. Because she was robbed of her voice, others must speak for her and for all of the others who are still taking Yaz pills. Do you all think this is some kind of academic debate? Are you seriously debating whether independent studies are trumped by Bayer studies? If there is even a question that there is more risk with these pills, we needed all of this? If there are so many questions about whether these pills are more dangerous, what are we doing here?

Because of all the alternative pills, the questions alone tell us that these pills must be removed. In my mind, these drugs should be removed from the market tomorrow. By leaving them on the market, you are confusing the situation. My daughter is dead, because Bayer confused the situation. Please fix this. No one would think that responsible scientists would allow that. It is worse than insanity. It is a sickness called greed. My daughter did not need Yaz. Bayer needed Yaz. And as for me, I need my daughter back and you can't give her back, but you can, you absolutely can prevent other mothers from coming here with broken hearts. Please remove these drugs. If you don't, you will answer for it.

Julia Johnson: If speaker number 10 could come to the podium? I'm sorry. Number 11. You are correct.

Bud Gerstman: It's tough to follow that. Good afternoon, my name is Bud Gerstman and I'm a Professor at San Jose State University. Early in my career, I was a public health service fellow and epidemiologist at FDA. I'm currently serving as an expert for the plaintiffs at multiple district litigation. I've been given three minutes to comment on the conflicting results of the studies shown in this slide. Clearly, that's not possible.

So given the time limit, I will focus on one aspect of the study design that has not yet been adequately addressed. Whether EURAS' use of non-idiopathic cases obscured differences between drospirenone and levonorgestrel. None idiopathic cases of VTE are those with alternative proximal cause such as recent surgery, trauma and so on. By including such cases in studies of drug associated risks, causal associations that might otherwise be detected will be obscured.

This is due to the interdependencies of component causes. Rothman and Poole (ph) recommend studies in low-risk populations as a way of uncovering hidden causal associations under such circumstances. This is a simplified numerical illustration the diluting effects of including VTE cases with alternative proximal cause. I'm afraid I'm not going to have time to go after the numerical explanation, but the inclusion of unrelated cases will dilute the difference between groups. This is not due to confounding.

To test this hypothesis of the inclusion of idiopathic cases, I have reanalyzed the EURAS data after excluding non-idiopathic cases. Clinical summaries were provided by Bayer and were sanitized of the references to the type of OC formulation used. A blinded review by an independent reviewer was used to determine concurrent conditions based on objective criteria. Denominator data were derived from EURAS sources.

This slid summarizes results of my reanalysis. Originally, the EURAS study had an unadjusted relative risk of 1.1. You can the numbers of cases and person time on the slide. After excluding non-idiopathic cases, the relative risk was 1.4. After further restricting the source -- the population (inaudible) 45, the decreased background rate, the relative risk was 1.6. This reanalysis supports the hypothesis that inclusion of non-idiopathic cases with alternative cause may have obscured the association between DRSP and VTE in the EURAS cohort.

These are some other design features that could also influence the results of EURAS. Don't have time to talk about them. If you have additional questions, here's my email address.

Julia Johnson: Will speaker number 12 please come?

Emily Moore: Good afternoon. My name is Emily Moore (ph) and today I will be sharing Kristen (ph) from Suwanee, Georgia's story.

I was one of the lucky victims of Yaz. I am a registered nurse, so when I began having symptoms of deep vein thrombosis in early July 2007, I knew I had a clot. I was and am a non-smoker and athletic. I run, lift weights, ride my bike or practice yoga five to six times a week and I'm height and weight proportionate.

On the recommendation of my gynecologist, I had begun taking Yaz 10 months earlier for relief of pre-menopausal symptoms. She told me, "Yaz is a low dose. It'll helpful regulate your hormones and you'll sleep better." I explained that I had never had a good experience on the pill. And she said, "This is a new one." The clots started as a pain in my calf. Because I'm so physically active, I thought it might be a strain. I worked (inaudible) with a neurosurgeon in the hospital and I'm on my feet a lot.

After three days, I was about 99% sure it was DVT. I called my internist and immediately went on heparin to prevent from worsening. Again, I'm lucky. I'm a medical professional capable on recognizing signs and symptoms. I know how to treat common life-threatening medical conditions. On top of that, I work in a hospital. I have quick and easy access to doctors, am fully insured, so the high costs of ultrasounds to diagnose the problems and medicines to treat the clot, were not a barrier for me.

The kind of heparin I was prescribed and could inject myself, Lovenox, only comes in 10 day lots which could cost about $1,500. After the Lovenox, I had to take another blood thinner, coumadin. While on coumadin, I had to monitor my titers regularly, which meant drawing my blood twice a week for the first two weeks and then once a week after that for about three months. My doctor wanted me to take coumadin for six months, but I got him to agree to half time. Because of the risk, I could not exercise for those three months.

Three and a half years later, my left calf is still enlarged. The clot is still there. In fact, it may never go away completely. But I am lucky. I was able to catch it while it was still below my knee where the chances of parts breaking off and turning into a pulmonary embolism are much lower. And I am glad it happened to me and not to my daughters. Both my daughters, one newly married, and the other who is still a teen, who are also taking Yaz. One had been on Yaz for about a year and a half, and the other for almost a year.

After what happened to me, they both decided to other safer pills. Not everyone taking Yaz is going to be a registered nurse. But with so many other pills on the market, you don't have to be in the medical profession to reduce your risk of being harmed by a blood clot. All you have to do is pick one of the other pills with half the risk of Yaz. Realistically though, how many teenage girls or women will know what to do. Are we expecting their doctors to warn them? Certainly, none of the three of us in my family were ever given warnings by our doctors. For that reason, I believe Yaz and all birth control pills with drospirenone should be removed from the market and by the FDA.

Julia Johnson: Now to move to speaker 13. If you'd come to the podium. Speaker 14?

Katie Anderson: Hello. My name is Katie Anderson (ph). Five years ago when I was 16 years old, I had irregular menstrual cycles. My doctor told me that birth control pills would help. I had seen the TV commercials for Yaz, which really caught my attention, with how they said it would help my PMS symptoms and acne. What teenage girl wouldn't want to take a pill that promises all that? So I told my doctor that I wanted Yaz and I walked out of his office with some sample packs and a prescription.

After six weeks of being on Yaz, I had developed a pinching, numbing feeling in my upper left leg. I awoke one night gasping for breath with an excruciating pain in my chest. It wasn't until a few days later when my entire leg had turned purple and I had lost all blood circulation in it, when my mother realized that I had a blood clot and rushed me to the hospital. If she didn't have a prior understanding of the signs and symptoms of blood clots, I might not be here speaking with you today.

At the hospital, I was diagnosed with a two and a half foot long deep vein thrombosis and a pulmonary embolism and found myself being life flighted from my local hospital in Frederick, Maryland by Medivac helicopter to Children's Hospital in Washington, DC, where I spent the next two weeks fighting for my life. After being released from the hospital, I spent months trying my hardest to get back to normal. The first weeks were spent in a wheelchair and after that I used a cane.

I was told that there was a 75% chance that I would never get full use of my leg again. I wasn't even strong enough to stand in the shower alone. I endured months of physical therapy. I couldn't finish the school year with my friends and had to have a home tutor. Almost most five years later, I still suffer the effects of the DVT and PE. I come from a very optimistic and mind over matter upbringing, so I was determined that nothing was going to stop me from anything until I was forced to accept the realization that my options for the future were going to in fact be limited by what happened to me.

Despite my best efforts to not let it, Yaz has affected me in more ways than I want to admit. I've had to give up on my dream of becoming a cosmetologist because I'm not supposed to stand for more than an hour at a time. I fall behind my friends when we're out hiking or swimming at the quarry. I've been called brown leg and made fun of because of the compression stocking I have to wear. Each time I'm faced with a potential challenge due to my leg, I force myself to push through it and fake it as much as I can. But I always pay for it the next day; sick and exhausted with my leg propped up.

Yaz has also affected my dream to one day become a Mom. If I ever get pregnant, I'll have to be on blood thinners again and on strict doctor's supervision and I don't know if I can go through all of that again. My disability has been unbelievably hard to accept,

but I do what I have to do. I wear my compression stocking every day and make trips back to the hospital anytime I'm feeling symptoms again. And every time I go, it brings back painful memories. This has been the hardest thing I've had to face and I'm reminded of it every single day.

What makes it harder to accept is that all of this didn't have to happen. I never knew the risk of the blood clots were greater in Yaz than for any other birth control. My doctor didn't even know that. I understand now that Bayer knew about the studies that show Yaz is more dangerous than other pills and they didn't --

Julia Johnson: Speaker number 15 please.

Adriane Fugh-Berman: Good afternoon. I'm Adriane Fugh-Berman. I'm an Associate Professor in the Departments of Pharmacology and Family Medicine at Georgetown and I direct a project called PharmedOut, that advances evidence based prescribing and educates healthcare professionals about pharmaceutical marketing practices. My conflict of interest disclosure is that I've been a paid expert witness is litigation regarding pharmaceutical marketing practices of menopausal hormone therapy.

Contraception is an important contributor to women's health. The most effective birth control methods are hormonal and the birth control pill is the most popular of all contraceptives, accounting for 89% of all dispensed contraceptives in the outpatient retail market. Oral contraceptives have been widely used for almost half a century and over the years, estrogen doses decreased and there has been a plethora of formulations. There are more than 30 oral contraceptives sold on the U.S. market. Many are available in generic formulations.

In 2010, about 84 million hormonal contraceptive prescriptions were dispensed in the U.S. Drospirenone-containing birth control pills constituted about 16% of that market. Two and a half million patients, which is about one out of seven of patients taking combined hormonal contraceptives received drospirenone-containing products in 2010. The astounding market share that Yasmin and her progeny achieved in a saturated market is entirely due to promotion.

Drospirenone has been touted as a unique progestin. Only Yaz goes beyond birth control, trumpets a 2007 ad. The possibility of weight loss was implied. The manufacturer gained an indication for acne, which most oral contraceptives treat equally well. There are dozens of randomized controlled trials showing that other oral contraceptives are effective for treating acne, but it's not worth it -- it was not worth it for manufacturers of older contraceptives with generic competition to seek a new indication.

And so it was very clever of Yaz's manufacturer to seek this indication. Nonetheless, Yaz has never been shown to be superior to any other oral contraceptive for acne. Yaz also received an indication for PMDD. A condition invented previously by another drug manufacturer. There's no reliable evidence that symptoms attributed to PMDD are more effectively treated with Yasmin or Yaz than any other contraceptive. Drospirenone contraceptives are -- the Yaz family is really an example of what industry calls evergreening or changing formulation to extend patent life.

It's been unique in its warnings even from the beginning. The Yasmin family of drugs was always more expensive and more troublesome than older generically available oral contraceptives without offering any significant advantages. In recent years, it has

distinguished itself. It does appear to have unique characteristics after all, a unique ability to harm healthy --

Julia Johnson: Thank you. Speaker 16, could you come to the podium?

Kirsten Moore: Good afternoon. My name is Kirsten Moore and I'm President of the Reproductive Health Technologies Project. Our mission is to advance the ability of any woman of reproductive age to promote her health and control her fertility. We do not accept any money from for profit companies or makers of drugs or devices. So we want to also thank the FDA for allowing public comment at this meeting.

And as advocates of women's health, we're very pleased that the FDA continues the safety and efficacy of contraceptive methods. This ongoing review is necessary to determine whether the risk profile of any given method reaches a tipping point that outweighs the health benefits of that method. In the United States, 43 million women are sexually active and do not want to become pregnant. Earlier this year, the Institute of Medicine confirmed what women's health advocates have said for years. Helping women and couples plan a pregnancy is beneficial to individual women, to children, and families, to communities, and to our nation's health.

But like any medication or medical procedure, contraceptives also carry risks. Not all of them are slam dunks like Plan B. Studies consistently indicate that all combined hormonal contraceptives carry some small increased risk of cardiovascular complications. And a growing body of evidence indicates that drospirenone-containing birth control pills confer an enhanced risk of these complications. The science concerning the safety and risks of drospirenone-containing pills is complex, so several factors should be considered in weighing how you, as the committee, should proceed.

First, the relative risks associated with drospirenone could be considered in several contexts including comparison with other hormonal contraceptive pills, comparison with other FDA approved medications and comparison with risk of cardiovascular complications associated with pregnancy. Second, it is important to consider whether and for whom drospirenone pills provide a unique benefit. Finally, it will be important to consider the role and effectiveness of clinician's screening and counseling in providing women with information about contraceptive methods.

We believe the FDA should consider action to ensure that all women considering or using drospirenone-containing pills are fully informed of the risks and benefits and encouraged, where appropriate, to consider other lower risk alternatives. Such action might include a combination of risk communication and management strategies such as prohibition are direct to consumer advertising, FDA consumer directing clinicians to risk data, and discouraging first line use, and the addition of a black box warning or other significant labels.

A woman chooses a birth control method for a variety of reasons and changing reasons and it's critical that a broad range of methods remain on the market. Thank you for your consideration.

Julia Johnson: If number 17 could come to the podium, please.

Pamela Bridgewater: Good afternoon. My name is Pamela Bridgewater. I'm a Professor of Law at American University, Washington College of Law. I'm a tenured full professor. I teach reproductive health law and regulation and protection of reproductive interests

and reproductive regulation and the history of race and class. I'm also a former Board member of Our Bodies, Ourselves, formerly the Boston Women's Health Book Collective, an organization which receives no funding from pharmaceuticals. An organization that has 40 years of experience as educators and advocates on behalf of women and girls and their sexual and reproductive interest.

There's no conflict of interest. And I'm here today based on my background and training law students and lawyers in litigation strategies when evidence of danger as to women's and girls' reproductive and sexual health arise. Specifically, I've long focused my pedagogy on issues such as the history of public policy and the legal implications of testing and marketing of birth control and reproductive health processes. I've written in this area and will continue to do so in fulfillment of my professional duties as a lawyer, a public interest lawyer, and law professor.

There are serious concerns that have arisen in the context of birth control testing and marketing. As our work indicates, as well as the compelling testimony today, oral contraceptives are very important to women and girls and the trust these women and girls place in us as public figures is comprehensive and at times has been well placed, but we all have an interest in making that the trust -- that we maintain a regulatory framework for monitoring our fulfillment of their trust as both policymakers and litigators.

The process for testing and marketing at issue today presents serious threats to these duties and I urge that questions such as the role the private sector interest played in bringing these products to market, and well as shareholder gains played in the process of marketing decisions. Specifically, a question of particular urgency is why did the studies that had the closest ties to Bayer show no evidence of an increase in blood clots? The FDA and public officials and lawyers in the public interest and the public interest bar and advocates in reproductive --

Julia Johnson: We'll now move to our final speaker, number 19 if you could come to the podium.

Elizabeth: Hello. My name is Elizabeth and I came here today with a prepared statement, but decided to change that. Back in January after suffering from pelvic pain for a long time, at age 42 I was prescribed one of those newer oral contraceptives. On day 51, I was admitted to the hospital with PE. At the time of discharge, informed my OB/GYN of what had happened, if only for her to report the incident to the FDA. I was shocked to receive a short, dismissive, "Sheesh, I'm so sorry."

So I drove from North Carolina to report it to you today. Yes, I'm overweight and yes, I'm older than 35. I asked my provider about the risk she was willing for me to take. It's a low dose she said, the benefits will outweigh those risks. So believing in her, I trusted her professional opinion. I never took oral contraceptives before in my life. So with those 51 pills, my life changed, and the lives of my family have forever changed as well.

So if banning these drugs is not what you're going to consider today, please consider that prescribing providers should absolutely be made to meet a higher standard of care when delivering the detailed explanation of the heavy risk involved when choosing this option of treatment, regardless of age, clotting factors, blood pressure levels, weight and smoking history, because regardless of all of those risk factors, the risk of blood clots still remains too high to not be made crystal clear to the ladies who are subjected to the possible wrath of these drugs. Thank you.

Julia Johnson: Thank you to all the speakers. The open public hearing portion of this meeting has now concluded and we will no longer take comments from our audience. We're now to proceed to a summary presentation from the FDA from Dr. Lisa Soule.

Lisa Soule: Good afternoon. My name is Lisa Soule and I'm the clinical team leader in the Division of Reproductive and Urologic Products. You've heard a great deal of information over the last several hours and I would like to try to provide you with a high level summary of FDA's perspective on the risk benefit profile for drospirenone-containing COCs. I will very briefly recap what you've heard about the product's effectiveness as a contraceptive.

I will highlight the assessments Dr. Ouellet-Hellstrom has made of the epidemiologic data relating to VTE risk and provide our current view of what we can and cannot conclusively determine from these data. Finally, I will present an overview of the issues we would like you to discuss and in some cases, vote upon today to help guide us in determining what, if any, regulatory action should be taken.

As demonstrated in registration trials, DRSP containing contraceptives are efficacious contraceptives with a Perl Index in the range generally found acceptable by FDA for hormonal contraceptives. Additionally, these products have various secondary indications including acne, PMDD, and to raise folate levels. These indications were approved based on review of clinical data. Initial concerns about the safety of DRSP contraceptives arose from spontaneous adverse event reports. These suggested that reports of death and ATE, especially strokes were more common in users of DRSP containing COCs.

The two studies required post-approval reported no increase in risk of VTE for DRSP COCs compared to contraceptives with other progestins. Most of them were recently published studies as well as the FDA funded study, have reported increased risks of VTE for DRSP users, compared to women who use other contraceptives including those that contain levonorgestrel as the progestin. The increased relative risk was seen particularly in younger women. It is important to remember that almost all of the studies discussed today evaluated only Yasmin and not the lower estrogen dosed products like Yaz or Beyaz.

Dr. Ouellet-Hellstrom has provided a detailed examination of factors and study characteristics that may have impacted the risk estimates obtained in these studies. Use of different claims databases result in differences in age and other population characteristics. Different database may also have differences in access to various comparator products and VTE appears to vary by the comparator studied. Some studies were able to define quite specifically a population of new users. This cohort tends to provide the cleanest risk estimates because it is not impacted by survivor effects.

That is women who are susceptible to VTE typically have an event early in the course of their use and then discontinue use of CHCs. Thus, those who continue using CHCs are women who may be at a lower risk of VTE. Variables such as BMI, personal and family history of VTE and smoking are important risk factors for VTE, but generally were not evaluated in these studies. Other factors may also confound the association of DRSP use with VTE risk but are not well enough understood to be evaluated.

And as you've heard, channeling refers to selective prescribing. That is targeting a specific COC toward a particular subset of patients. There's some evidence that Yasmin is preferentially prescribed to women with certain conditions such as PCOS. Adjusting for some comorbid conditions decreases the relative risk of VTE observed for drospirenone. It is possible that channeling may account for some of the increased VTE risk observed for drospirenone.

FDA has conducted extensive review of the studies reported to date. The majority of studies suggest that Yasmin appears to be associated with an increased risk of VTE compared to COCs with other progestins. However, as discussed, there are many factors that may impact the risk estimates obtained in the various studies. It is important that future studies or reanalyses of the data we already have evaluate the impact of these factors. We cannot draw a firm conclusion about whether Yasmin is causally associated with increased VTE risk until we have fully assessed this impact.

Nonetheless, in the face of uncertainty, FDA is often called upon to provide guidance to healthcare providers and patients and we seek your advice today on how best to do this. Based on the data you've heard, we seek your thoughts on the following issues. First, what is the impact of differences in study population, comparators, exposure definitions, handling of confounding and possibly channeling bias on one's ability to compare study results?

Should some of the studies or findings be given greater weight than others? Are users of drospirenone containing contraceptives at an increased risk of VTE compared to users of contraceptives containing other studied progestins? Do the benefits of drospirenone-containing contraceptives for prevention of pregnancy outweigh the risks? If not, are there subpopulations for whom the risk benefit profile might be favorable? Finally, does current labeling adequately reflect the risk benefit profile of drospirenone-containing contraceptives? And I just remind you that the current labels for these products are included in the FDA background package. We thank you for your consideration of these important questions.

Julia Johnson: Thank you. The committee is not going to return to questions directed towards the sponsors, so we will go back to the individuals who had asked to ask questions of the sponsors. As we go through this, if you have additional questions for the sponsors, please raise your hand. After we address the questions to the sponsors, we will then return to questions to the FDA. So Dr. Stovall?

Dale Stovall: Thank you. My first question -- I have three. I think they can be asked and answered very briefly though, very quickly. First one had to do with some data that was shown looking at relative risk over time and I think it was three month blocks, zero to 3 months, 3 to 6, and so on, and it showed relative risks increased in the first three months, not in the second, and then again in the third, if I remember correctly. It was described as an S-shaped variable or outcome, if that does help. It's been a little while.

And my question was this. I think the data was used to make the point that there's less likely that there's a causal relationship in between drospirenone and VTE. And my thought would be that that isn't necessarily the case. That certainly it may be that there are different mechanisms might cause the problem; those that perhaps in the first three months simply an increase in clotting factors makes a difference would have an event. But others that may have other impacts with less vascular, whatever that might be, may have an event that happens further down the road. That was my first thought. Could you comment about that?

Leo Plouffe: Sure. The first thing I am trying to show the slide. We're having some technical issues, so some reason the -- we're projecting the image, but it's not coming up on the screen. So I think we may -- we're seeing what's on the screen and not the other screen, if that helps our technical colleagues there. Let me attempt to answer still while this is going on. So in terms of I think the primary point, this was part of Dr. Makuch's presentation on the FDA trial and it was addressing a specific statistical element in the analysis. So I'll be glad to have Dr. Makuch come back and address exactly what he was underlining.

It is interesting though, in terms of the studies, when you breakdown the groupings, this was not done in the EURAS trial, but it was done by Dr. Lidegaard in his reanalysis, for example, where he broke this down. There is a lot -- the patterns he saw in these studies are opposite to that. So I don't there is any biological plausibility there. I think it's more the tierney (ph) of small numbers, if you wish, as things are being looked at. In the EURAS trial where we have large numbers, we do see the primary events occurring during the first six months, especially during the three months, but the numbers are very, very consistent across the board there and they're seen for all COCs.

And in the case of EURAS, the risk is similar at all points for all COCs. So I do think this is -- it is tempting to look at some biological explanation here, but I think this was more of a statistical point. I'll be glad to have Dr. Makuch come and address it if you wish.

Dale Stovall: No, I think that's -- it makes good sense to me. The next comment or question I had, you showed some data looking at effectiveness for contraception particularly and there was a few histograms looking at Yasmin versus other products showing an increase in the effectiveness of Yasmin. And I just wondered, were those head-to-head data or not head-to-head data?

Leo Plouffe: Yeah, so these are indeed head-to-head data from the INAS study. So as you know, the INAS we're following women as I demonstrated with different cohorts. So we're following women on Yaz. We have a cohort on Yasmin. And then we have the women on other COCs. The data presented were data published earlier this year in the Green Journal Obstetrics and Gynecology and they did also breakdown among the other COCs for 24/4 regimens, not containing drospirenone and other 21/7 regimens.

So it's really a very unique dataset at this point, providing life experience. Now, we have to remind everyone, these are women who consented to be part of the INAS. So this is different than just a general population. But in this context, it's as close to a naturalistic head-to-head comparative study you can achieve.

Dale Stovall: Thank you. And the last comment I had was, we had a little bit of presentation looking at the benefits and the attractiveness, if you will, of this option compared to others. And however, it didn't seem to make sense when I looked at the persistence rates. There was a publication from the Green Journal that showed about 50%, I think, persistence after six months, if I remember correctly. Could you speak to -- how would you explain that low rate of persistence?

Leo Plouffe: I think, as you're well aware, and we can have this slide up if you wish. I think that's -- I want to make sure I'm referring to the slide you were looking at Yasmin. Is that the one?

Dale Stovall: That's right.

Leo Plouffe: Okay. So I think in general combination oral contraceptives in the country tend to be preparations that women will use intermittently. So the average days of therapy is highly variable. So I think the important thing here is to look at the comparator group in this study and the -- what you want to look is how it compares to other pills in terms of the persistence from that perspective. There's clearly a number of reasons that women interrupt using their COCs. Many time because they decide they wish to get pregnant.

But in terms of the tolerability perspective, the other data I showed on Yaz or may be a little bit more telling, because what we're looking at women being on one pill and switching to another pill, and the lower switch rate means that on Yaz there's better tolerability because they definitely wish to continue with contraception. They elect to -- which pill they continue on.

Dale Stovall: Thank you.

Julia Johnson: Dr. Morrato?

Elaine Morrato: Thank you. I had two questions. One with regard to sort of study enrolment in the EURAS and INAS, and the other with regard to the concept of channeling bias and what you shared is some data on the preference ratio data. So as others have mentioned, kind of struggling with trying to understand the differences between trials that might account for the differences in the outcomes. And one thing that came to mind was that the EURAS and INAS are consenting studies.

So these protocols in which women have to consent; for some, up to 10 years they're being followed up. And I'm wondering whether that in of itself might be introducing some bias in terms of the types of women that are participating in these surveillance studies, i.e., are they more health motivated, more higher education, higher socioeconomic, et cetera, and whether or not might have an effect on perhaps shifting the results more towards the null effect.

I'm struck by the fact that the Women's Health Initiative Study, for example, has taught us that the importance of this healthy user effect. So I'm wondering if you could comment. If you've looked at the types of -- what was the consenting rate in your studies and what were the characteristics of women who did not consent versus did participate, and where there any meaningful differences particularly between U.S. and maybe European.

Leo Plouffe: Right. This is question of a high level of interest. We've done several things. In terms of gathering the information on individuals who did not consent and individuals who did consent, unfortunately, we've not come to a good way of doing that, since they have to be consented for us to start gathering the information on them. So any help or insight on that would be highly appreciated. What we did look, Dr. Dinger and the group at the Center for Epidemiology and Health Research did look across several of these large studies at the population that they recruited in the trials and compared the information they have on those individuals to general characteristic of the population where the women are recruited.

And in terms of the range, in terms of income, socioeconomic status, ethnic distribution especially in Europe -- we're also tracking other elements, in terms of those

elements the percentage wise, the recruitment in the cohort mimics very much the national level. So it does appear we're recruiting, for example, only high socioeconomic level individuals in the cohort or university educated individuals or something like that. We really seem to be gathering a broad cohort of individuals.

Now, that leaves unanswered the question, who consents to participate in the study for five years and we don't have an answer. And again, if anyone has good study methodology to really sort that out, obviously it remains an element. So that's important. I do want to highlight that in the Ingenix study, that is in our mind one of the strengths of the Ingenix study because there you access anyone that's in the United Healthcare formulary. You have to use a very different approach, which is propensity score, to achieve a good match, but that's the advantage of that type of study. So I hope that answers your question.

Elaine Morrato: That's a good start, yes. The other question I had was with regard to -- you talked about this preference ratio data, and you referred back to data that was collected in the late 1990s, I believe in the U.K. and Germany, if I recall. Survey data that was gathered shortly after a 1996 statement from the U.K.'s committee on the safety of medicine regarding the combination contraceptives, and finding that there was channeling or selection following that kind of warning.

I'm trying to relate that to where we are here today in the United States. So I'm wondering if you have any internal data -- this was published, but if you have any internal data, I would imagine marketing or market (inaudible) kind of data, either qualitative or quantitative that might speak to this notion of channeling bias or preference. And not only among physicians, which is what this study was, but also among patients? Because I would expect that with direct to consumer advertising that's drawing a lot of demand, patients coming in asking for specific contraceptives and that may be partly also influencing what might be channeling. So do you have any data?

Leo Plouffe: So to my knowledge, we do not have any data like that that would inform on channeling. I think Dr. Ouellet-Hellstrom pointed out in the briefing document, unfortunately the studies, even those referred to by Dr. Grimes, are all European based. So we agree we need some information on that.

Probably the more reliable information was some of the information that was gathered in the FDA briefing document. For example, looking of PCOS women -- was there a differential prescribing? And I think roughly 50% of these women, small number, but 50% of these women seemed to be on Yasmin as opposed to other OCs, but that's about the extent of the information on that we have.

Elaine Morrato: So no market research data that's supporting the advertising material development that's been done to like at preferences?

Leo Plouffe: Not that I'm aware of. We'll be glad to look into that specific information. The marketing focus of research generally does not tend to be in those elements, but I'll be glad to look up that information and we'll share it with FDA.

Elaine Morrato: That would helpful I think. Thank you.

Julia Johnson: Thank you. Dr. Winterstein?

Almut Winterstein: I think Dr. Grimes provided a table on Slide 47 that I thought was helpful because it summarized all these various biases that we talked about and that we are trying to consider in evaluating the studies. What I was disappointed about was that there was a little bit selective discussion of the various aspects of this, and that the FDA study was omitted. So what I was wondering, whether you could help or Dr. Grimes, to focus on two studies which I think are really good for many reasons.

First of all they both were done in the United States. We have both PIs sitting in this room. And I consider both of them of very high quality. So that's the Ingenix study and the FDA study. So if we take those two studies and we walk through these various aspects of bias here, I actually cannot help but think that they are quite strikingly and that the only difference I see is if the Ingenix study has less power, it cannot out rule a risk of up to 1.9, which of course includes the risk estimate that the FDA has.

So what I was wondering, is it we go through this and I hope that I got all of this straight with respect to the study methods. If you're looking at the pattern of use, I think the biggest issue here was that if we're including periods of non-use into the use, so we are essentially doing some type of interaction to treat analysis, we would water down the effect and bias the study towards the null. Now both studies do present to us and as used analysis, so that should be actually similar between the two studies. I was not totally sure in Dr. Seeger's write up, whether current use was actually including switchers as well, so that there basically was time dependent definition of exposure which might actually produce a little more channeling in this, because I think the propensity score (inaudible) was just done at baseline.

But beyond that, both studies should actually be similar in the definition of this, with attrition of susceptibles or depletion of susceptibles, so this issue that in particular in the older generation users, there are more women who are not new users and thus -- and basically have survived their first year exposure, both studies took care of this to the same extent in such that they excluded women who had at least six months of eligibility in the health plan. And the important part is we are looking here at Kaiser Permanente versus UHC, so I would imagine that the (inaudible) population is actually quite similar.

So I don't think that there is a differential bias between those studies from what I can tell. If you're looking at channeling, the FDA study is the one that's actually providing us some estimates of the comparability of those two groups. And what we see is that the Yasmin users have less hyperlipidemia, less hypertension, are younger. Even though we don't see exercise and smoking, my sense would be that it seems that this is the healthier population, which would, of course, mean that Yaz is actually, or Yasmin is actually -- has an advantage.

So even if there were residual bias, it doesn't really seem to go in the direction of elevating a risk. And both studies looked at the similar risk factors and had the similar ability to adjust for those. And then we're going -- the last issue that was brought here was this issue of misclassification of the outcome, both studies used an ascertainment algorithm that was based on claims data and both studies validated this. And again, misclassification, if it is not differential, would bias the study results towards the null, meaning that again the FDA study really didn't have any way in increasing the risk more so than Dr. Seeger's study would have done.

And then lastly, which is what is not here on this list, would be the choice of the comparator and they seem to be quite similar as well as such that different does of

estradiol were included. So if you could just comment on what I just said and whether I left anything out that I'm missing that would explain to me why Dr. Seeger finds no risk and FDA finds a risk with respect to these biases and I wish you could explain it me, but the only thing that I can come up with, basically Dr. Seeger doesn't have the same amount of power.

Leo Plouffe: So I think the key element, I think I would agree at a high level. We could dig to the detail just to make sure we're fully aligned, but I think we're aligned in your high level assessment of these risk factors. I do think a key element those differences what we pointed out on the previous slide, which is making sure you start off with balanced cohorts. And this is where I think the power of a propensity scoring methodology may be preferable in this type of approach. So I would call on either Dr. Makuch or Dr. Seeger if he wants, since he's here with us, to just explain maybe how the cohort was done. But I think that's the key difference between the two studies. Dr. Seeger, do you want to address?

John Seeger: Hello, I'm John Seeger. I'm from the Brigham Women's Hospital in Boston. I'm compensated for my time here today. I'm here to represent the Ingenix study and thank you for pointing out some of the similarities and very little differences between the Ingenix study that I conducted as was a part of in conducting with my colleagues and the FDA study that I have no association with.

So I can restrict my comments to explaining what we did in Ingenix study which was to -- we had a new user design and it's been pointed out how new user is defined differently by different people. Our new user was new user of whatever oral contraceptive women were starting at the initiation date. So we didn't use naïve users exclusively. It was a mix of switch new users and naïve new users. And then we used an intent-to-treat analysis as well as a time on drug analysis and the results were remarkably similar.

So that switching after the start of follow-up did not seem to be an explanation for our finding of no difference in the occurrence of venous thromboembolism. I wanted to make one more point, which was about the -- not available data on past use or long-term past use of oral contraceptives. This was partially addressed through our valuation study where we obtained medical records at the time of initiating oral contraceptives for women in both the Yasmin initiator cohort, as well as the comparator cohort.

And in that study, we found -- we looked at age at first use of oral contraceptive and were able to show that was reasonably well balanced as our proxy for past use, so that these groups were balanced with respect to past use of oral contraceptive, even though they were a mix of initiation and switch initiators.

Almut Winterstein: May I make one follow-up comment on the --

Julia Johnson: Yes.

Almut Winterstein: Okay. So the fact that -- just to put this in perspective where this bias would go to, not having cleaned your users, since we see that the Yasmin users are younger, their propensity for being a new user would be higher and we know that new users have a higher risk for VTE, so the trick would be to try to get the comparators as much new users as possible. So since the FDA study did a little bit better job with this, it actually balanced the playing field a little bit better than the Ingenix study, which again would

mean that the FDA study should actually have the lower risk -- a risk estimate that's closer towards the one. Would you agree with that, John?

Leo Plouffe: I think that's where -- I was asking Dr. Seeger just follow-up in terms of the actual propensity approach to the study, because I think it's really important to understand how we achieve balance between the cohorts. That was then validated for the VTE issue.

John Seeger: That's right. Even though ours had a mix of naïve new users and switched new users, the balance was even on that. And even with respect to things that aren't captured in the claims data -- the long-term use, so that the balance was even in our study and that's what I can speak to.

Julia Johnson: And let me ask you -- did -- although we're addressing questions to the sponsor, did you have a question that you wanted to bring to Dr. Sidney at the same time, since you're comparing these two studies, or can that wait?

Almut Winterstein: As long as Dr. Sidney thinks that I've summarized everything correctly of what they did, I think we are fine in this regard.

Julia Johnson: Dr. Kaboli?

Peter Kaboli: Yes. I had a question for Dr. Grimes. As you stated, in spite of your incomplete and superficial description of bias in observational studies, I really thought you did an outstanding job of outlining the limitations of observational studies and potential bias. In fact, I think you've done such a good job that I'm going to give up my pharmacoepi career, because there's no way I can publish again at the level of rigor that you're asking. So you made me wonder why the BMJ actually published two of papers. I mean they're a low tier journal, but they did publish these studies.

So related to this and really what I wanted you to answer is, are you saying that we need to have randomized controlled trials to detect harm? Because if that's the case, we're going to have to have enormous sized trials to detect harm and not be able to use observational trials.

Leo Plouffe: Can I ask you to specifically state your question, sir? Are you asking -- Dr. Grimes assessment of the -- there are four BMJ papers, first of all, so are you asking the --

Peter Kaboli: Well, let me ask this question. Is he advocating that we should have a randomized controlled trial, because that's what he said upfront? That the only way to overcome these biases is to have an RCT. So do we need a -- because one of the questions that we're going to have to be faced with is, do we need additional trials to answer the question of harm here? So are you advocating that we need an RCT to detect harm for these drugs?

Leo Plouffe: So I'll let Dr. Grimes answer that specific question, then I can provide --

David Grimes: No, I agree entirely. One cannot do a randomized controlled trial of very rare events like VTE. And pharmacoepidemiology has a clear and important role to play in research. However, I do ascribe to the guidelines that were promulgated by the FDA earlier this year, that we need to go back and validate these VTE diagnoses in source documents at the patient charts. You've seen in the problems in the Danish database. There is just a lot of misclassification.

Peter Kaboli: Right. But there would have to be some systematic misclassification and as someone who takes care of lots of patients with VTE and studies it, I can't see how there's possibly that there's a misclassification bias for VTE diagnosis.

Julia Johnson: Okay. Dr. Kittelson?

John Kittelson: Thank you. Can I come back to the propensity matching and because we're going to have to try to debate what's gotten us closest to a randomized controlled trial in these areas. The thing you don't have in the middle of a trial often is advertising about one arm of it when people know what they're on. So you have the winnowing, the channeling was another one and then advertising, that all controlled behavior on many different levels. I seem to remember reading in these many pages, something about also a time matching in the propensity scoring. Could you just give the briefest overview of what the key features of the propensity matching were, so we can get some idea of what the key considerations were in making that match?

Leo Plouffe: I can provide just high level. The cohort -- the propensity score really took into account over a hundred variables and these are already well known to the FDA. I'm sure they be shared. It included obviously the age, the date of entry into the database. It looked at demographics and type of reimbursement, any prescription medication use and this is the United Healthcare database -- it was comprehensive, any medical diagnosis and again a long list, utilization of health services and laboratory tests, not just the result, but actually the effect of having the laboratory test.

So these were all the elements built into the original propensity score matching. And just to be totally transparent, these were selected initially focusing on the antimineralocorticoid activity of drospirenone. In terms of the cohort, they were assembled on a quarterly basis. So slide up. It's a little bit of an eye chart, but I think it does get the message across. So at the beginning of each quarter, a new cohort was initiated -- one for the users, and one for the other COC users, and that continued during the entire period of the study. So the match was reestablished at each quarter (inaudible).

John Kittelson: At each quarter. Okay, thanks.

Unidentified Participant: I'm a little pent up over here, so I'm going to claim that I'm asking one question with several parts. I have the same interest that a lot of my colleagues have in understanding what the additional benefits might be. And I was wondering if either the sponsor or Dr. Lukes or the FDA people were aware of a systematic review published in May of 2011. It's an update of a 2004 systematic review, types of progestins and combined oral contraceptives, effectiveness and side effects.

It's an overview of 30 trials, only four of which were blinded. And they come to the conclusion that without blinding as to treatment group, comparisons between the various generations of progestins used and combined oral contraceptives cannot be made. So I would ask whether they're aware of that and whether that's the sort of evidence we should be looking at? Not the odd study here or there about acne or PMDD.

Related to that, that kind of systematic overview and synthesis is what I'm longing to see on this adverse event side. And I wondering of the sponsor whether Slide 49, I was just dying to see at that end of that -- that's the one where you layout all the -- what the

combined estimate looked at. All of cautions about combining aside, I just was dying to see what it looked like and wondering if you had done that?

Secondly, I received a lot of communications from the consumer community about allegations that Bayer had been withholding data or that its major studies suffer from conflict of interest and I'd like to hear the sponsor address those.

Julia Johnson: These are wonderful questions. Perhaps let's address them in order, but we will let you continue. Would you like to deal with those first three?

Leo Plouffe: Sure. So in terms of the efficacy of the indication for PMDD and acne were both achieved through registration studies that were accomplished in collaboration with the FDA and that meet the standard for accomplishing these type of studies. The registration studies were placebo-controlled and that's the context that the registration were achieved for both the indication for moderate acne, for PMDD. There are additional studies that have been conducted on the area of acne, particularly comparing drospirenone to other antiandrogenic progestins which are not available in the U.S. And those studies, while small, and underpowered, do show a preference -- potential higher level of efficacy for Yaz compared to other OCs and we think that's an area that needs to be explored more.

So in response to your question, do we need more head-to-head trial in the area? I think the answer clearly is yes, but in terms of the rigor and the scientific rigor behind the design of the acne trials and the PMDD trials, they were very comparable to other medications approved in the area of acne and in the area of PMDD, comparable to other trials not just in the -- it's the only COC approved for PMDD, but the other trials in PMDD were SSRIs versus placebo. So that's the common area there.

So would we appreciate more data? Absolutely. Is there a need for more head-to-head trial? Absolutely, but we do stand behind the quality of the studies that have been done up to now.

Unidentified Participant: But you are aware of the systematic overview?

Leo Plouffe: Yes. The next question. If we can have Slide 49 I believe. In terms of hoping to see one integrated number for this, I'm no statistician, but I believe this would be well, would not be well advised. It would be giving the impression of having some type meta-analysis when there are significant differences across these studies and that's the main purpose of today is to helping understand the differences between the studies and resolve them. So I don't think this is something we would engage in. We have not engaged in to it up to now. So just to be clear on that one.

In terms of transparency of information, we've been focusing on this advisory committee to make sure we provided you with all the background information. As part of that, we've had an opportunity as a team, to review extensive communication over the years with the FDA. To the best of our knowledge, we've always had a very open communication. We've responded openly to all the requests for information from the FDA and the information were presented in today is in total openness. So I hope that puts your mind at rest at as committee today and obviously if you have any questions, we'll be glad to provide any additional data.

Unidentified Participant: I'm trying to find my other -- are you aware of meta-analysis and formal sensitivity analysis by Hennessy et al at the University of Pennsylvania 2001, Risk of venous

thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel? It's a method of, despite all the caveats, of trying to deal with combining this kind of information and --

Leo Plouffe: I am not familiar with that particular article.

Unidentified Participant: It's an approach that could be taken, I think, to go a little bit beyond saying it's -- you know, it's not possible to combine these data. I highly recommend it to you.

Leo Plouffe: We'll be glad to look at that and consider it.

Julia Johnson: Did you have other questions?

Unidentified Participant: I had a question about both the follow-up data and the age data and whether it's possible to and whether you tried to model those as continuous rather than categorical variables and if it made any difference?

Leo Plouffe: Sorry. Would you indicate which study you're referring to?

Unidentified Participant: I'm forgetting which slide it was where you showed the length of follow-up data and the difference in the risk of VTE by duration of use.

Leo Plouffe: I think you may be referring to the slide from Dr. Makuch. The same slide that we showed for Stovall was it?

Unidentified Participant: I'm think so. I'm getting lost in my notes.

Leo Plouffe: I'd rather that Dr. Sidney comment on that, as we're the -- slide up. Is that --

Unidentified Participant: No, it was a bar graph. Three, six, nine and 12 months.

Julia Johnson: Perhaps we can hold that one for the FDA. Other questions.

Unidentified Participant: The comment was made during the public comment period about a long list of other countries that have conclude that the risk is higher with drospirenone-containing pills and I was wondering from the FDA folks if that's true? And if so, are there data that they're looking at that we're not looking at?

Unidentified Participant: You know your labels as well as I do. Do you want to comment on it, because there have been some recent changes? Certainly the EMA has made -- back when we issued our data safety communication, they did come to the conclusion that the -- in their opinion, the risk was higher than that of a levonorgestrel containing oral contraceptive and they said it was, in their opinion, similar to that of a third generation product. I don't believe that that same statement, however, was made by other countries. Perhaps the U.K. reached the same conclusion, but I don't think it's universal. Would you like to comment on that as well?

Leo Plouffe: Yeah, I'll be glad to ask Dr. Bettina Fiedler who's our global regulatory lead on this to comment on this. I do want to point out, to put it in a U.S. clinical context, that especially the label in Europe has historically and really since the mid-1990's drawn a clear distinction that the risk with third generation progestins is higher than second generation progestins. So the background label for second and third in Europe is very, very different than what we're seeing in the U.S. Whereas, all of you know the U.S.

label very well, it says that some studies show an increased risk, others do not. So it's a very different situation. So in that context, it's important to understand the context of the EU labeling and Dr. Fiedler can also comment on Australia and other labels.

Unidentified Participant: I'd just like to follow-up briefly. In our data safety communication, we had alluded to all these other studies and we had indicated that were we to go ahead and change our U.S. label, we wanted input from this committee. And so we're, as Dr. Soule has indicated, and as I have indicated, your guidance today will be very helpful in any labeling changes that we might be making subsequent to this meeting.

Bettina Fiedler: Good afternoon. My name is Bettina Fiedler. I'm from global regulatory affairs at Bayer and you quote the European label quite correctly, so for the benefit of the committee can we bring the slide up, please. As you said, the current label, as it was changed in May of 2011. So in May of this year, it reads that "epidemiological study have shown that the risk of drospirenone-containing OCs is higher than for levonorgestrel containing COCs and may be similar to the risk of desogestrel and (inaudible) containing COCs." And this is the label in all European member states, because the products have been approved within a Europe procedure.

Now this has to be seen as, Dr. Plouffe pointed out, in the context of the European specific label situation going to the gestodene and desogestrel discussions, if we can bring the next slide to familiarize with the approach the Australian Health Authority has taken. This label change dates back to September 2011. In principle, the first two paragraphs are similar to what you have seen or what you are seeing in the documentation for the U.S. label. The additional information that was included in 2011 refers to a study of Heit et al giving the general rates of VTE risks in the general population. So in the non-user population also and in the pregnant and postpartum population.

And then what has been added as well, are the two studies that were published in August 2011 in the BMJ by Parkin and Jick, quoting that there suggestion for higher risk. And last but not least, let me also bring up the next slide please, which gives you the Canadian label that has actually only been updated as of last week, which basically again takes the approach of summarizing the epidemiological study that you are already familiar with from the U.S. label. And then in addition, can we have the next slide up please, it goes on to say that these studies suggest a potential 1.5 to 3 times higher risk of VTE. However -- but prescribers should consider the benefits and risks for specific patients with respect to VTE risk.

So all in all, we can say that the approach the difference health authorities have been taking around the world is not unilateral the same and the European one is certainly the shortest and strongest warning which has to been seen in the context of the European situation.

Julia Johnson: Dr. Schisterman?

Enrique Schisterman: I have two questions. Number one, originally the cohort studies that you designed, were designed with certain power to detect effects. Can you allude at the fact, because a null finding implies two things? One is that it's not there; the other one is that there is no (inaudible) the sample size to detect something. The second thing I wonder, clearly you show on Slide 49, that the meta-analysis wouldn't be something favorable to your studies. It's clearly seen to be a decreased risk, but did you take the opportunity to look into a meta-regression where other factors that you're raising into -- as being the factors

that differentiate between your studies and the non-sponsor studies are the ones that explain the differences. I wonder if you can comment on those two points. Thank you.

Leo Plouffe: In terms of your first question, the EURAS study, and remember the EURAS study was designed in close collaboration with the EMA upfront. So the upfront power for the study was an 80% power to detect a two-fold or greater difference between Yasmin and levonorgestrel OCs. So that was the upfront. As the corollary of that is if it proved that there would not be a two-fold or greater, then a less than two-fold difference would be demonstrated and that's indeed what's demonstrated with the upper confidence interval.

In case of Ingenix study, remember the situation was quite different, because Ingenix was already underway when the FDA approached Bayer about including a VTE analysis in the study. So in that sense, the original power calculation were done monitoring events related to hyperkalemia or potential for elevated serum potassium. Ultimately, the confidence interval generated from the Ingenix for the assessment of VTE is really what we're relying upon for the ability of the study to provide the point estimate in the upper confidence intervals. I hope that answers your question.

In terms of any further analysis, we very much welcome suggestions from the committee today. We see this as a great opportunity to discuss the science. Again, the reality is when we're looking at this list of trials, there are significant differences in each of the studies. Two of the studies there looked only at non-fatal idiopathic cases. So our approach up to now has been to not to try to amalgamate all those and generate a single number, but we're very open and we look forward to suggestions and we'll definitely be open to then working further with the FDA at looking at how these analyses can be conducted. We're as anaphylaxis as anyone to resolve the differences and get to the actual estimates around these issues.

Julia Johnson: Dr. Gardner?

Jacqueline Gardner: If I could back to labeling again, Dr. Lukes I think was, at the end of her presentation seemed to suggest that there was quite a clear direction in the existing labeling of a three to nine-fold range of increase in VTE risk associated with OCs. I've been all over the packet insert since then, the one we were given, and I can't find that. I can construct approximately a three to approximately 11 range of relative risks, depending on which subgroups within the labeling I'm able to pull out.

Of all those though, they talk only about all oral contraceptive products and when we move into discussion of Yasmin, no numbers are given. Really only they were comparable to other OCs. And so in the interest of clarity, since I can't find it, I wonder if you had a slide showing me approximately -- so we can get the context of the risk communication as we look toward our fifth question here. And -- well, I'll stop there for now.

Leo Plouffe: Yes, so apologize for any confusion that may have been caused Dr. Lukes presentation or our presentation. If we can have slide up, what Dr. Lukes is referring to is the language that is currently in label conveying with is the risk of VTE. So not a relative risk, but what is the risk of VTE for women using COCs? And the risk is given as 3 to 9 per 10,000 women years.

Jacqueline Gardner: I apologize. I have in front of me, the Yasmin label.

Leo Plouffe: And you're correct that the Yasmin label is not yet in PLR format. All of our other labels have been converted to PLR format. The Yasmin label is pending update to PLR, but what you're referring to is older studies as they were conveyed. The more recent label and the most recently approved COCs have the language that I just put up there which is conveying the specific number. And if you look at the Yaz or Beyaz label, that's the information that's in there.

Jacqueline Gardner: Sorry. So once again, this is for all oral contraceptives in this context?

Leo Plouffe: That's correct.

Julia Johnson: Dr. Montgomery Rice?

Valerie Montgomery Rice: Dr. Gardner, I'm glad you brought this up, because I thought maybe it was just me, because I've been reading this label over and again and I couldn't find this information and I still can't find it. So if you bring up Slide 110, I think this is what confused me in Dr. Lukes study. Slide 110? Because this is what I saw here, this 3 to 9. So you're that this is in all oral contraceptive pill package inserts --

Leo Plouffe: All -- well I won't comment -- I think with our colleagues from the FDA here, they're in a better position, but all recently approved COCs I believe have that statement for the range of event. Dr. Soule?

Lisa Soule: That's correct. All of our COC labels that are in the physicians labeling format have that language.

Valerie Montgomery Rice: But everything has not been converted as of yet.

Lisa Soule: That's correct. The older products tend to be in the older format.

Valerie Montgomery Rice: Okay. And so my other part of the question was -- you were -- what were you trying to indicate from this slide?

Leo Plouffe: I'll have Dr. Lukes come and speak to her slide. You can leave the slide up, please.

Andrea Lukes: So what I wanted to understand was kind of regardless of the studies strengths or weaknesses, et cetera, what was the actual crude rate that they found in terms of 10,000 woman years. When I provide counseling, I do say it's usually twice the risk, up to nine. The package insert goes over the Ingenix and the EURAS study and the two initial studies within the British Medical Journal. So the additional studies there give the crude rates per 10,000 -- 9.3, 7.9, and 7.6. And if I explain it correctly, then some of those are statistically significant more because the comparator group, levonorgestrel is sometimes too low, lower than what you would otherwise expect.

Valerie Montgomery Rice: So on the other slide where we have 123, that this is the Yaz label then, Slide 123, and so we're not talking about Yaz, Y-A-Z today, but this is the most up-to-date label for Yaz?

Scott Monroe: Yaz and Yasmin essentially have the same language in today's label, as least as it pertains to the specific risk related to drospirenone. In our drug safety communications of May and I believe it was September -- was that the second one or was it October, we did give specific numbers. Here, you won't find the specific numbers and if you

continue to look, you still won't find them. That's one of our questions today to this panel. And as you've seen, there have been two different approaches taken,

One was by the EMA where they made a sort of summary conclusion, looking at the totality of the information and they came out with a bottom line conclusion that drospirenone containing oral contraceptives, in their opinion, posed a greater risk than levonorgestrel based products and was comparable to third generation. I believe both Australia and Canada, and that's why I didn't specifically answer your question, I prefer that the company show the actual wording, has taken a somewhat different approach, the same approach that we used in our drug safety communications, where they basically listed the outcomes of the six studies or so. None of which include anything from the FDA study, which our drug safety communication did.

And in our questions to you, where we ask you if you feel that labeling revision is warranted, one of the follow-ups to that is we would like your opinion as to whether you think just listing the outcomes or reports from the various studies would be an appropriate way to communicate any increased risk? Or whether you think it would be necessary or best for us to try to come to a bottom line conclusion? And in doing that, again, there are earlier questions that we're posing to you. If you as a panel feel that looking at this disparate data, we can come to such a bottom line conclusion.

So I think our label right now, it could be the way it's going to be, but we're also going to hear from you as to what your recommendations to us are. And I don't want to second guess what they will be, but I'm sure you'll convey your opinions to us shortly.

Valerie Montgomery Rice: So Dr. Monroe, I appreciate what you just said, but we get information and we got a package of information from you all and I have been looking at that this was the label that is in the document here. I haven't bought birth control pills for a while so I don't know what -- I haven't looked and saw what the package insert actually says, so can you give me some clarification, if a women buys a birth control pills today, what will be in the package insert? Is this in the package insert? No, right? But this has been approved to be in the package insert and we just hadn't printed it yet? Clarify please.

Unidentified Participant: This is in Yaz. This should be in Beyaz and Safyral.

Valerie Montgomery Rice: Pardon?

Unidentified Participant: This language is in Yaz, Beyaz, Safyral, all of which are in the PLR format.

Valerie Montgomery Rice: But not in Yasmin.

Unidentified Participant: That's correct, because that's (inaudible) --

Valerie Montgomery Rice: What's in Yasmin is what is in our package here?

Unidentified Participant: In your package, you have the current labels for -- I believe for both Yasmin and Yaz. So those are both today's labels in your package.

Valerie Montgomery Rice: Okay.

Scott Monroe: Dr. Soule is right, but there is a nuance. The reference to drospirenone and potential risk -- the labeling is almost virtually identical, even in Yasmin. It doesn't have a nuance about starting and stopping, which is a little different and that's unique to

Yasmin. But as far as the findings from the EURAS study, the Ingenix study and the two studies that were published in 2009, virtually the same working is in Yasmin and Yaz in reference to that.

The label does not include the information that was published in 2011, which we've communicated through our drug safety communication mechanism because we honestly felt that was the best way to communicate this new information, because it comes out as an FDA announcement, which we felt gets it better attention than just doing a labeling change. And also, we felt that, because again, as we've said several times, the disparity of the findings, we wanted input from this panel.

So it is in there and it's under section, it's in the warnings section, Dr. Montgomery-Rice and it's under thromboembolism which is, I think, section B, so you'll see that same warning. It's -- if you look there or I can help you with you later.

Julia Johnson: To ask the committee, I would ask if it's possible for the sponsor to pull up that portion of the current labeling, not for now, but when we're discussing that, that would be very, very useful.

Leo Plouffe: I want to make sure I understand. You're talking about the specific language about conveying the information on the studies? That's correct. Yeah, and we can bring it up if that's convenient now.

Julia Johnson: Yeah, when we get to that point of discussing labeling changes, then that would be useful to have that projected on to the screen.

Unidentified Participant: If I could just make on other clarification, because I don't know if it's completely clear to everybody, our labels tend to be a composite of class labeling, which is identical information for all combination oral contraceptives and then other smaller areas that may be specific to a given drug, or in this case, a given progestin. And so I just want to make that clear. So the 3 to 9 per 10,.000 women that we were talking about, is class labeling that is in all COC labels that are in PLR format. But I think what you're focusing on now is the drospirenone specific section of the label.

Julia Johnson: And just to clarify again, the PL -- that the new labeling is everything but Yasmin.

Unidentified Participant: Yes.

Leo Plouffe: Which is pending, just to be clear.

Julia Johnson: Yes. Okay. Now Dr. Hernandez-Diaz?

Sonia Hernandez-Diaz: I had very similar questions (inaudible) so I'm going to focus on only one that I would like to expand and that's regarding the adherence and the intention to treat analysis and the (inaudible) analyses. So I don't know if you want to answer or maybe Dr. Seeger wants to answer them. With the adherence that you had presented in some of the slides, expected to be around 50% or 60% after three months or so, and with the studies going on for over six months, you will expect like half of the patients not being on the initial medication during the follow-up and that will tend to (inaudible) intent to treat analyses.

Then you have the (inaudible) analysis, that if the misclassification in the intention to treat is true, you'll expect it to produce stronger associations if there is one, but you

don't find one. So I was wondering whether in the as treated analyses, you adjusted somehow for who remain on the specific oral contraceptives after time. In addition to the additional propensity score matching, if you did any kind of adjusting or controlling for goes on the pill. I'm going after the possibly of perhaps the as treated analysis being also biased towards the null for who survives (ph) in the medications.

Leo Plouffe: Let to ask Dr. Seeger to come up and answer that question.

John Seeger: All right. I think it will be helpful to have Slide 27 from my presentation. Okay. So these show tables from our intent-to-treat analysis and our as treated analysis that show the incidence rate among the Yasmin and other OC cohorts broken out within periods of use following initiation in the cohort.

And we show that most of the use is in the current use time in both cohorts. That is after initiation of the cohorts, after the start of follow-up, the amount of follow-up that we have is fairly limited and during that follow-up time, there's actually fairly little switching between the cohorts. And there's actually fairly little complete cessation or oral contraceptive use during that follow-up time. So that the intent-to-treat analysis in the top table here, is largely an as treated analysis.

Sonia Hernandez-Diaz: So the adherence was better than one would expect based on other studies.

John Seeger: The adherence was pretty good, but I'd say that's a little bit artificial compared to sort of longer term follow-up that is -- the amount of follow-up that we have is about seven months in each of these cohorts and so there's less time for change than there might be in longer follow-up study.

Julia Johnson: Thank you. Dr. Suarez-Almazor?

Maria Suarez-Almazor: Yes, I have two questions. One is about risk and the other one is about benefit. So I'll start by the risk one. If I can have Slide 53 of the sponsor's, please? CC53? Okay, this slide shows preference ratios between all (inaudible) and second generation pills. So I was wondering if Dr. Grimes could explain to me what does this mean with respect to the Yasmin product? That study or survey was not done for Yasmin. So is the assumption here that Yasmin is being prescribed to women who have more risk factors to start with?

David Grimes: Yes, that's correct. During the second versus third generation controversy in the 1990s, there was concern that much of this might be due to prescribing bias with the newer, ostensibly safer pills being preferably prescribed to women at higher risk. And the study here you'll see done in Germany and also the one done in the U.K., suggested that physicians were indeed prescribing the newer pills to women perceived to be at higher risk of VTE and other cardiovascular outcomes. We have evidence in the EURAS that this did indeed occur. Women who were obese in the EURAS study were 60 to 80% more likely to be prescribed Yasmin than were other pills.

Maria Suarez-Almazor: Then I would respectfully like to suggest the sponsor cannot have it both ways. If we look at Slide 60 which examines misclassification, much of the criticism of the registry based studies that are not sponsored by industry hinges around the validation. So if we look here, the impact of misclassification, if it's random, if it does anything, is basically decrease the risk. So for instance if we look at the study by Lidegaard, the relative risk was two, so if the misclassification had indeed occurred at random, the risk would probably be higher, even higher than two.

On the other hand, there might be systematic misclassification, but if the sponsor believes that actually the patients who receive Yasmin had more risk than the others, if anything again, these registries are underestimating the risk and not overestimating it.

Leo Plouffe: Sorry. I think there are two elements there. So I think what Dr. Grimes was addressing was prescribing bias. And in terms of prescribing basis, is again are you comparing two different populations that have different underlying risk or are you comparing the risk with two medication? So if there is a preference in prescribing for one pill versus another, that's the concern we have. And to be candid, when we were conducting the EURAS study, we knew there was some degree of prescribing bias that Dr. Grimes has reflected, but otherwise, the cohorts were well matched. With the propensity score matching, they were matched as well.

Maria Suarez-Almazor: Yes, I did not explain myself fully. I'm sorry. What I meant is that the assumption was made that the validation was systematic because probably the DVT and the PE cases were under reported in one of the groups compared to the other one, because of some press that had been in the news about the Yasmin product or the DRSP product. I don't know any of the two products.

So the assumption was made that at that time, practitioners may have felt that the DRSP products were more risky and that's why they did not report the DVTs. And a lot of the criticism that was made around possibly systematic validation was based on that. But if we look at the data, if anything practitioners felt that Yasmin and the similar products were more safe. So if anything, they have been less likely to report that.

Leo Plouffe: So they're two separate elements, albeit connected. The concern in terms of the diagnostic bias is that if somebody presents how likely are they to have a full diagnostic algorithm all the way to be diagnosed, and how likely are they to be treated. The one set of data we have is from the EURAS study and if we can have the slide up. So if we look at the EURAS study of individuals who self-report VTEs, so remember the context of these women, but if we look at women who self-report VTE, how many ultimately are confirmed as having a VTE. It's roughly 30% in the Yasmin cohort, compared to 37 and 39% in the other OC group.

So what we're saying there is that in the absence and in EURAS, all the cases go through full case validation with clinical chart review and blinded ascertainment. So our concern is that individuals -- so if somebody presents multiple risk factors for VTE, they may be more likely to be suspected of having a VTE and that could drive a diagnostic bias. So there are two separate biases. One is on the prescribing side and that's why we think that's very important and then there's one on the diagnostic bias side and both of them are very, very important to take into account.

Maria Suarez-Almazor: Okay. And my other question that relates to efficacy, I'm still struggling a little bit with what the benefit of these drugs might be, because any risk as small as it might be, it's only worth undertaking, is there some benefit that you can gain? So I would like to ask the sponsors with the evidence that's available you can unequivocally state that you believe Yasmin is more effective than other contraceptives.

Leo Plouffe: We're not making any -- we're making claim that Yasmin is a very effective contraceptive and it's approved for that purpose. So in terms of Yasmin, it's an effective contraceptive. We do think it offers a range of choice and it allows

physicians to have a dialogue with their patient as to which pill they wish. In terms of Yaz, you have the additional indication of PMDD which is the only COC that has that indication and also moderate acne.

Case of Beyaz and Safyral, Safyral is the Yasmin version with the folate addition to raise serum folates, and so Beyaz is also the Yaz version with additional folate. So those are really the main elements. And at the end of the day, I think -- already Dr. Soules presentation shows that these are effective contraception. She's talked about the overall benefit risk and what we're advocating is to provide the information to clinicians and then allow them to make the decision.

Maria Suarez-Almazor: Yeah, but my question is not whether they are effective. It's whether they are more effective than the other alternatives in the market?

Leo Plouffe: Well, at this point, we're still gathering the data. That was not part of the commitment for approval. The approval is really to show that there an effective form of contraception. As I repeated, there are preclinical and pharmacologic studies that show that a 24/4 regimen is better at keeping -- inducing ovulation suppression and because drospirenone has a long half-life, it has a 30 hour half-life, that means it's a pill that is potentially more forgiving than other pills if you skip a pill. So these clinical pharmacology studies involve comparing two regimens.

So both drospirenone regimen, one 21/7, one 24/4, and in that context looking at what happens if you skip three pills with the 21-day regimen, if you skip three pills at the beginning with the 24-day regimen. If we can have the slide up, if we look at this you can appreciate and these are clinical pharmacology studies, but they underlie the biology behind the findings. If you look at this during the second cycle, this is taking the pills exactly as would be directed. So a full course of 28 day pills; 24 for one regimen, 21 for the other. And you can appreciate that from the onset, the additional four days of therapy appear to cause a high level of ovarian suppression.

The second one is the missed pill cycle where the first three pills, the first three active pills of the cycle, are skipped. So it's a pharmacoepidemiological experiment to reproduce what may happen if people skip pills and you can appreciate here that you have an almost comparable to taking the regular regimen with the 24/4 regimen as opposed to the 21/7. So that's, in part, the support behind a 24/4 day regimen being better. The evidence that drospirenone may confer more efficacy is what we're continuing to accumulate through the INAS trial.

Maria Suarez-Almazor: Okay, but if I ask you -- and just to choose as effective or more effective, what will you choose on the basis of the evidence? Just one choice.

Leo Plouffe: In terms of the evidence right now as reflected in our label, I have to say it's as effective.

Maria Suarez-Almazor: Thank you.

Julia Johnson: I'm just going to remind the committee that we need to move to discussion fairly soon. We want all these questions though to be answered. I'm going to allow another 15 minutes for questions. We'll be as effective as we can in getting all of these answered. Next, Dr. Bockman?

Richard Bockman: I have a quick question and it's the other, Dr. Plouffe, it's the other side of that question that was just asked. It has to do with harm. Trying to remove those who might be in harm's way. Does your company have any ongoing studies looking at what possibly makes certain individuals more at risk from a hematologic point of view?

Leo Plouffe: The studies were conducting right now, as I mentioned we have three large scale ongoing studies, the INAS OC, the INAS Score and the INAS Focus. We're constantly looking at what could be markers or predictors. At this point we've not been able to identify any clear area that would help us focus that attention. So again, if there are suggestions from this committee, we'll be glad to consider them.

Julia Johnson: Dr. Wild?

Bob Wild: Maybe Dr. Makuch might help with this question. I need to know more about the propensity score. As I heard you, there were like a hundred different variables that were involved with that scoring. Is that correct?

Leo Plouffe: In this particular propensity score methodology, yes. Dr. Seeger may be able to have --

Bob Wild: So my question is, is how were those derived at? You said that it was shared with the FDA?

Leo Plouffe: Yeah.

Bob Wild: And then how was that dealt with in the analysis? What did you do about overmatching? And what is the -- was the analysis blinded and was the same for every comparator study that we're looking at? And how was the adjustment made in reference to what those concerns are?

Leo Plouffe: Let me to ask Dr. Seeger to comment.

John Seeger: All right. To help, we might have the Slide 3 from my presentation. For the propensity score, it was developed independently for these 12 different cohort accrual blocks. And so in each of these different propensity score models, we had a set of core covariates that were always included and then we had some that were sort of exploratory based on perhaps changes in the way Yasmin was prescribed over time and that could be in response to say changes in advertising or changes in the literature.

But then the matching was done also independently within each of these blocks. That is the propensity score is develop, the matching was conducted, and then propensity score analysis as we used it was a two stage step. There's first this matching process and then we form the cohorts. And after that has been matched, we don't take into account that matching further. That is the matching process balances all of the covariates. You can do a very straightforward analyses after that. And so that's the approach that we used.

Your question about overmatching, we matched on a very tight caliper of the propensity score, but we're balancing on exposure related variables, rather than outcome related variables, as in a case control study where you really do worry about overmatching. In the case of the propensity score, cohort matching, you don't worry as much about the overmatching.

Bob Wild: Yeah, but you have to worry about that in the analysis. So my question is in relation to the analysis, and your matching, how was it handled?

John Seeger: The analysis was pooled across the cohorts, forming a pooled cohort, but what we did was then -- there pooling all of the Yasmin initiatives and pooling all of the comparators, and the analysis then balances all the cohorts that were matched on the propensity score individually within these pooled groups. I think that's -- so that's the explanation of how we handled it there.

Bob Wild: So you did not adjustment because you matched well?

John Seeger: So the adjustment was, there wasn't a further adjustment. I'd actually say it that way. We just matched and then the balance was achieved through the matching.

Bob Wild: And in relation to some of the other studies, you mentioned your modeling, COX modeling I think it was, of concerns in some of the other studies because of a lack of some of variables. I'm interested in how the analysis differences were done in relation to when you did propensity matching versus when it was not done.

John Seeger: Sure. So we did the analysis two ways. We used a COX proportional hazards model for the intent-to-treat analysis. And then we used a Poisson regression analysis for the as treated analysis. With the Poisson regression, we had a limited number of variables that we could account for on top of the matching and these would be the kinds of variables that might affect switching, so they had to be accounted for even within these balanced cohorts.

Julia Johnson: Dr. Woods?

Mark Woods: Dr. Suarez-Almazor went somewhere that I wanted to go, and that had to do with when Dr. Soule began her presentation she talked about efficacy. If you look at the sponsor's Slide 104, when I first saw that, I was a little taken by, gosh why would Yaz and Yasmin be different? But then I looked closely and they're not. But why did you choose to split those out and then why did you choose to lump every other oral contraceptive product together as a group. Because when I looked at that and thought about it, it really would imply that you do see fewer contraceptive failures with the DRSP containing products. But I think you said a few minutes ago in answer to her question, that's really not the case.

Leo Plouffe: So just to distinguish, there's one element about the evolving science and the other element is what we would say according to the label today. According to the label today, all oral contraceptives are effective. There's no distinction from one oral contraceptive to another that one is more effective. In terms of the data, the reason separating out the analysis for a 24/4 versus a 21/7 is because of the underlying biology that I described before. So if you look at, if we can have slide up, which is another way of looking at it. So there's several ways you can look at this.

These are all in the publication, but this is comparing the 24 regimen, the 21 day regimen and the other oral contraceptive cohort. And we have also breakdown, for example, of 24 compared to 24, and 24 compared to 21 and 21/7. So let me show you this one to start with, but if you look at the cohort here, there is statistically significant difference between the 24-day Yaz regimen and the other OCs. If we come to the next slide, this is comparing the two currently available 24-day regimens. So this

comparing Yaz to nortestosterone acetate ethinyl estradiol as a 24-day regimen. And there again, you see a difference.

We continuing to focus on this and that difference would show if you look at both of these 24/4 day regimen, if you put all the curves, it gets real confusing, but both 24/4 day regimens are better than 21/7 day regimens. It's not acknowledged right now on the labels. It's science in evolution. If you look Yasmin compared to another 21-day regimen, next slide, you can see now comparing two 21/7 day regimens and the data you have there. So the idea was not to pick one slide. We were trying to avoid a lot of complex graphs. The paper again has been published. All the analyses have been shared. But the ultimate scientific interest right now is that 24/4 day regimens overall, may provide greater contraceptive efficacy.

It has yet to be established and demonstrated. Clearly, none of that is reflected currently in the labels. And then if we look among 21/7 day regimen, there may be a differential effect by the progestin. Again, none of that is reflected in the label. And I hope I stated clearly enough. These are early data right now from the INAS U.S. cohort. We're looking to repeat those data from the European cohort and also generate more information on this.

Mark Woods: Yeah, I don't think you misstated, but I think the construction of this to me was a little bit misleading.

Leo Plouffe: And I apologize for that.

Julia Johnson: Dr. Hewitt?

Geri Hewitt: I'm a clinician and I have a question. You know most -- your data suggests that most patients that are using drospirenone containing birth control pills are using it primarily for contraception, even though there are other indications, they're primarily using it for contraception. And we know historically that when desogestrel -- there was a concern with those about the -- in Europe or the U.K., there was a quicker and stronger warning about desogestrel products and that resulted in a higher rate of unintended pregnancy.

And I'm wondering if Europe or the U.K. now is having a quicker and stronger response to concerns about drospirenone. Do we know yet if there's been an increased rate of unintended pregnancy and do we know anything about what the change in their product labeling has done in terms of prescribed practice and use and unintended pregnancy rate?

Leo Plouffe: It's a confusing area. So right now, no, this happened in May, so we don't have any information as to what's happening. It is of interest to note that in Europe, I already highlighted that in Europe, the label clearly states that third generation have a higher risk than second generation. Yet, the use of third generation in Europe, they're the preferred pill. So the use of third generation progestin is higher than most second generation pill and the use of levonorgestrel is very low. So it's a very difficult set of dynamics to understand at present.

Julia Johnson: We do need to move on to discussion. Dr. Espey?

Eve Espey: I just wonder to what extent that's marketing. Looking at the -- again in the United States it's the same thing. We have a very, very small share that's levonorgestrel and we had the same scare in this country about third generations. Certainly, in my

population, which is largely poor and undocumented, everybody gets Sprintec, which is a third generation, just because that's the pill that they can get for $9 a month. So I mean I think that there are other issues that go into what pills people use, but wouldn't marketing be the most prominent cause?

Leo Plouffe: Are you asking in terms of the European situation right now? I can ask Dr. Schellschmidt, who's my colleague for global medical affairs who has a closer understanding of the European marketplace that can comment on that.

Ilka Schellschmidt: Good afternoon. My name is Ilka Schellschmidt, Global Medical Affairs, Women's Healthcare. With regard to your question, there is no direct to consumer marketing in Europe. So all communication around combined oral contraceptives is done via the healthcare provider. So marketing in that sense, plays a completely different role than in the U.S.

Julia Johnson: Thank you very much. We do need to move on now to our discussions. We will --

Unidentified Participant: I'm really sorry, but I thought there was going to be opportunity or question for me from the panel, and I really feel, just in fairness, if I could have about two minutes. There were some critiques made of my study --

Julia Johnson: Just a moment, before you speak, was there -- let's -- people who feel they have questions that need to be answered before the discussion -- Ms. Aronson?

Diane Aronson: I have had a question for the FDA. First of all, a question. This has been put at our desk. Is this from the FDA?

Julia Johnson: It is not.

Diane Aronson: It is not.

Julia Johnson: That is from Dr. Wolfe.

Diane Aronson: Okay. Thank you.

Sid Wolfe: It's IMS data from --

Diane Aronson: Okay. Well with the concern with the independent from the sponsor review by the FDA and then the emerging data that talked about a 77% increase, and then the prescription decline, which seems that the marketplace is saying something as well, as I was reading over all the documents before I came, I saw the Phase I and Phase II and I thought, well, how can we effectively come together and really have this discussion if there is all this Phase II still to be determined? I'm wondering if the funding is there, number one, for Phase II, how this plays out relationship to our discussion today and if it matters what happens today.

Unidentified Participant: Okay. So I can address the funding issue. We still have not yet worked out our funding for extramural studies at this point for this fiscal year which began -- as you know, the federal fiscal year begins on October 1st, so we're still working out what that funding would be and what the priorities for that funding would be across the wide range of drugs and safety issues we cover.

Diane Aronson: And that's what I was wondering too about the study design, whether there was any discussion about that.

Julia Johnson: So I believe the question is do you want us to look at study design, if we think that is needed?

Rita-Ouellet-Hellstrom: I think that your recommendation would be greatly appreciated based on discussions today. Whether we're able to do it or not, at least the scientific community can be thinking about it and can be providing some input to us as to what is needed.

Julia Johnson: And I hate to do this, but our time is very short. But very brief questions, and then we'll allow you to address issues. So Dr. Gilliam?

Melissa Gilliam: I have a procedural question. A number of slides said this is about Yasmin, no Yaz. Any comment we make today or decisions we make today pertain only to Yasmin, right? So it means these three others that we talked about aren't involved or data showing 24/4 is not relevant to whether it has a unique property?

Rita-Ouellet-Hellstrom: No, we're open to any recommendations or comments that you make. What we wanted to make sure was that what we were talking about and presenting today in the published data, only referred to the 30 microgram of ethinyl estradiol. Although the press has referred to a lot of these studies as Yaz as well as Yasmin, and we wanted to make sure that it was clear what data was available and discussed today. But we're welcoming any comments that you may have.

Julia Johnson: Dr. Monroe, did you have a comment?

Scott Monroe: Well, just that when you go through our questions, you'll see they're worded in a general sense and they refer to drospirenone-containing oral contraceptives. We just wanted to make it clear that virtually all of the data, except that for the INAS I think studies which the company presented, are obtained specifically with Yasmin. That's what we were just trying to clarify for you Dr. Gilliam.

Julia Johnson: Dr. Hennessey?

Sean Hennessey: Thank you. In preparation for the discussion about labeling, would it be possible to see what the U.S. desogestrel label looks like?

Julia Johnson: Yes, we did ask the sponsors to bring that forward for us.

Leo Plouffe: You have the U.S. desogestrel label? If my colleagues would bring it up.

Sean Hennessey: Specifically with regard to VTE. I don't know if we want to do that now or just have that available at the time when we're talking about label.

Leo Plouffe: I don't think we can project it. We can show it at any time as the Chair desires. Would you like it projected now or --

Julia Johnson: I'll tell you what. Let's hold until we get to labeling discussion. Thank you. Dr. Winterstein?

Almut Winterstein: At the risk of being nagging, I wanted to get back to the channeling one last time and we have two sets of data that propose channeling. One set of data comes from the

FDA study and it proposes in the direct to patient population where the analysis was done that Yasmin users were healthier and at less risk for VTE, which would suggest that whether you adjust for it not, in any way or fashion, that shouldn't be any bias towards coming up with an increased risk of Yasmin. The other data we have is physician surveys that were done in Europe that suggest that physicians self-report, that they are channeling towards more obese women, but this has nothing to do with the population that we actually looking at.

Now when Dr. Seeger did his propensity score algorithm, he must have had those hundred covariates and he must have looked at how those hundred covariates were distributed among the Yasmin users and his comparison group, an I was wondering whether he could share with us his observations. So essentially, a similar baseline characteristics table that was provided by the FDA for the FDA study, what was -- if you don't have those hundred covariates, I totally understand, and I also understand that it's hard to combine this since you've run the propensity score 12 times.

But nevertheless, pooling all of this together, did you see any indication that in the Ingenix data, Yasmin users had higher risk for VTE? Because if that were not the case, then the propensity score adjustment really doesn't matter.

John Seeger: Yes, if I can have my Slide 14? Yes, slide up. So as you suggested we have a table of baseline characteristics and this is a truncated table. It doesn't have all of the hundreds, but this has the ones that are common across the cohorts. And you can see these cohorts are largely young, healthy women and so there's a fairly low prevalence of almost all of these conditions. The propensity score balances them quite well, and -- but there wasn't a large amount of difference to begin with. The propensity score C statistic tended to be around 0.7. So that suggests there wasn't a lot of discrimination to begin with, but there was some.

Almut Winterstein: That's the matched version or the unmatched version? What I'm interested in is the cohort, the unmatched cohort.

John Seeger: So the 22,000 and the 44,000 cohorts are the matched ones. The 250,483 was the pool of available comparators.

Almut Winterstein: Okay. But we don’t have -- what I was curious about -- you're right. I mean all of those disease states are obviously are very, very rare. What I'm curious about, if you see similar pattern to the FDA study that hypertension is a little bit increased in the comparison group and obesity is a little bit -- well, they didn't have that. But the classic VTE risk factors seem to be increased in the comparison group and not in the group, which basically means that the adjustment isn't really that important in terms of explaining why the FDA finds an increased risk because it would bias in the opposite direction. Would you agree?

John Seeger: I'm sorry. I don't have the table that would maybe help illustrate that, but there was some difference and I agree with the characterization that there wasn't a large difference to begin with.

Almut Winterstein: Okay.

Julia Johnson: Dr. Sidney, did you want to make a comment?

Stephen Sidney: Yes, if I could make two comments. I appreciated the scholarly reviews by Dr. Grimes and Dr. Makuch, but they did level some criticisms at the study that, one of which I think is totally unwarranted, and the other thing I think was maybe overstated. And the unwarranted one is that there was no comparison of like to like. And in fact in the report, it's very clear that most of the analyses were also done with regard to levonorgestrel with 30 micrograms of ethinyl estrogen. You got it. So the same amount of estrogen, basically.

And the main analyses basically showed very similar findings, highly significant, slightly decreased relative risk, about 1.5 for VTE with all users and new users. All the sub-analyses were also done that way. So they're in there. They support them and they weren't hidden and I just wanted to point that out, that the like to like is in the very highly shown there.

The second thing has to do with adjudication and both them concluded that there was incomplete adjudication. We're very clear that there's incomplete adjudication for the outpatient DVTs. For the hospitalized events, whether it's MI, stroke, or VTEs, there's very high rates of adjudication. When you throw away the junk, more than 90% of the records were obtained for all of those endpoints and we show the analysis for hospitalized VTEs and all VTEs that they are about the same result.

Overall, even if you take the problem of the 120 or so that we didn't get our hands on from the other sides, it's still about an 80% adjudication rate. The Ingenix study had about a 90% adjudication rate. And one thing that has not been said here about the EURAS study, is as best as I can tell reading the paper, and maybe there's something missing, is that there were no medical records actually seen by the adjudicators. The process of case identification was the woman volunteering that she had a case of VTE, and you know there -- surprisingly people do get things screwed up, but I just want to remember that it's self-report. And the physician of that person was asked. And --

Julia Johnson: Thank you, Dr. Sidney. Appreciate the

Stephen Sidney: Perhaps there's more information on that.

Julia Johnson: Thank you. So now we have --

Leo Plouffe: (Inaudible) on EURAS. So medical charts were reviewed just to be clear on that. Thank you.

Julia Johnson: Thank you very much. So thank you to all of the committee members. Thank you to the sponsors. Thank you to the FDA and our guest speaker. Our time is limited. What we are going to do, we will now begin our panel discussion portion of the meeting. Although this is open to public observers, public attendees may not participate, except at the request of the panel. What we are now going to do is I'm going to read to you each of the areas for discussion and I would like to go through the table and give your comments to me. I will summarize them at the conclusion and get agreement on that summary. Each person's comments, if you could give in one minute or less, I would greatly appreciate that. So, shall we move to discussion one?

How do you view the impact of differences in study population, comparators, exposure definitions, handing of confounding and possible channeling bias on one's ability to compare study results, particularly across studies that reach different conclusions? Are there different confounding variables other than those presented that need to be

addressed? And I'm going to start on this side. Dr. Gut, would you like to give your comment? No. I apologize. (Inaudible) you would like to make a comment.

Unidentified Participant: Okay. Well, taking into account all comments, bias, and controversy around the study, I still see like consistent story with regards to VTE risk across the FDA trials as well as trials presented by Bayer. And as a physician looking at the incidence rates of VTE in -- not necessarily in (inaudible) I see consistency and I see this risk between 6 to 12 or 13 per 10,000 woman years. So I have clear picture here. Thank you.

Julia Johnson: Dr. Burke?

Anne Burke: So I feel like this is actually a big question and I'm not sure that I have a one minute answer to it. I definitely think there are still some issues across -- comparing populations across studies. And I think we've discussed earlier, some possible concerning factors that maybe haven't been addressed, like BMI, obesity and smoking. Nonetheless, it does seem, that several of the studies are coming to the conclusion that there may be an increased risk with the drospirenone-containing pills. That being said, I think the absolute risk is still low, but I don't think we can ignore the fact that the increase might be real.

Julia Johnson: Thank you. Now, Dr. Schisterman?

Enrique Schisterman: Yes. So clearly the (inaudible) on the possible confounding is an issue of concern. What is unclear to me and I -- it will be easily taken care of, is that one can take care of (inaudible) confounding that it goes unmeasured. So it's a little bit puzzling the fact that no analysis has been to evaluate the effects of unmeasured confounders. I mean there is tons of techniques. This is nothing that we don't deal in any other field. So the uncertainty of deciding if the evidence is strong or not, depends very much so on the effect of those unmeasured confounders.

And by a very simple analysis which is in every second year epi course, one could answer the level of uncertainty that unmeasured confounding will add. So I urge both -- most of the studies that have been presented to evaluate the effect of BMI and smoking and how the results will change if those variables would have been measured and if in fact the result will be null or away from the null.

Julia Johnson: Thank you. Dr. Raymond?

Elizabeth Raymond: I would echo Dr. Burke. The studies, the observed findings of many of these studies seem to show and increased risk, but I think bias also could account for some, most, or even possibly all of the differences observed. I think the -- if there is a difference in risk, it seems to me it would be relatively modest in absolute terms, considering that the absolute risk level is low.

Julia Johnson: Thank you. Dr. Hennessey?

Sean Hennessey: Thanks. I feel like I'm in the middle of the third versus second generation oral contraceptive controversy again, in the phase of it in which new studies continue to come out one after the other and that we need to get a little bit of space between a recent study and what the overall results are telling us. I think that in general, the results are probably -- the results of the different studies are probably more consistent with one another than inconsistent. The upper bound of the confidence limit from the Ingenix is consistent with the other results. I also think that the risk, if it's elevated, is

of modest degree in terms of absolute risk in the population. That's not say that individual people experiencing that event, don't experience severe even-year-old

Twenty percent of women who have a VTE have residual effects and it's got a case fatality rate of about 2%, so certainly a severe event. The other point is that the benefits of drospirenone-containing oral contraceptives over other marketed contraceptives are not demonstrated. They've been creative enough to show benefits versus placebo, but there haven't been head-to-head with regard to those benefits. I look forward to seeing additional data addressing the possibility of confounding and possibility of subgroup effects and I'll stop there. Thank you.

Julia Johnson: Thank you. Dr. Gardiner?

Jacqueline Gardner: I agree with Dr. Hennessey. I think that probably all of these studies essentially are showing an increased risk regardless of what we control for and don't, but I think it's critical that we obtain quantitative data on differing risks by subgroups, specifically racial ethnic subgroups if that's relevant, smokers if that's relevant, and people with differing BMIs. Not least of the reasons to help our understanding, but also so that people can be given warnings that they can work with, if we're going to ahead with these products.

Julia Johnson: Thank you. Dr. Tepper?

Naomi Tepper: I agree with the comments that were made that all of these observational studies are not perfect. I think all of them have strengths and weaknesses. It's hard to discount any of them and it's hard to discount any of them and it's hard to say that there's a not small increased risk of VTE with the drospirenone-containing pills. And I also agree with the comments that have been made that it's important to take these into context with the overall absolute risk that this represents in the population and also the risks pregnant and postpartum women.

Julia Johnson: Thank you. Dr. Wild?

Bob Wild: I think everybody agrees, observational studies have their challenges. I think there are significant differences and it's the old apples and oranges challenge that we all have. There's a common message and it should be in clinical risk. I think there are some important residual confounders and those could be built into a better look, if we have the opportunity through better funding. You wanted other ideas. One would be occupation. Are people active or inactive? We have a generation that's changing. They're sitting looking at computers. They're inactive.

As a clinician, I want to know about family history because that's how I screen people very carefully, because clotting does run in families. I want to know if it's just serendipity, there's a common risk and I sort somebody one reason or another, and to me that's important when I have to decide on those edges, not for contraception, but for abnormal urinal bleeding, for hirsutism, for acne, for all those fringe areas that we all use as clinicians. So yeah, I think we understand that there are problems, but we can -- with any observational study, but we can be really careful at trying to look at some of the challenges ahead of us.

Julia Johnson: Thank you. Dr. Suarez-Almazor?

Maria Suarez-Almazor: Yes, I again, I think the risk benefit aspect is important, but I don't think this question is addressing that. And with respect to this, again, the other studies are different, but I think there could have been an effort made into trying to pool or analyze the studies together to see what different impact of the various confounders had on the results, because there's enough data for that and I'm not sure there is the availability of obtaining primary data from the original studies to be able to do more analyses. These are the studies that are very expensive to conduct and there's a lot of data, but I don't think it's been looked in sufficient depth.

And the same I think is true for the FDA study. I think that it could be looked at with a little bit more depth and doing a little bit more of analysis around it to control for unknown confounders. And as far as the confounding variables are important, I mean there are many that could be important, but the easy ones together would probably be smoking, BMI and socioeconomic status which I believe is important when we are looking at drugs that are still brand name and are a little more expensive.

Unidentified Participant: Oh, the other thought that I had for other potential things to look at, do we have anybody to look at over-the-counter medicines and interactions? Is that totally beyond our grasp? And you talk about drug interactions. How many people are Aspirin users or contain headache problems that are -- you know I mean 50% of my patients take other things they don't even tell me about. How many are taking other hormones for other reasons, and how can we deal with that and those potential interactions. Obviously, we have a complex challenge.

Julia Johnson: Thank you. Dr. Hernandez-Diaz?

Sonia Hernandez-Diaz: I believe that these factors are important and can explain differences (inaudible). However, in this case, based on the data that we have discussed today, I don't think there is strong evidence to support that these factors will explain the association found in some studies and that adjustment for some of these factors will result in lower relative risk or could move the rate of risk enough as to move them closer to the null. For example, the different populations in the studies where we were able to indirectly assess the potential impact of this difference, we didn't find evidence. For example, we talk about the potential different relative risk in different populations.

However, when we showed results for Medicaid Tennessee populations, or Kaiser Permanente in California, for VTEs, the relative risks were very similar. Or when we discussed the impact of validation, probably better evaluation, if anything, could have resulted in stronger associations. When we discussed the confounders, we didn’t see strong evidence for confounding being an important factor in the propensity score or in the European study and (inaudible) could actually result in lower rather than stronger relative risk. When we discussed the adherence problem, we saw the intention to treat or the as treated analysis gave similar results.

When we discussed the importance of a new user design, which I think is an important thing to conduct, but we didn't see in this case, any strong impact of conducting the new user design. So in conclusion, I think that these differences are important, but it's not clear to me with the data that we have, that they will move the relative risk up or down or in other words, the null in those studies that found an association.

Julia Johnson: Thank you. Dr. Wolfe?

Sid Wolfe: The FDA has done some things obviously in this drug, such as getting labelling on, and here we are as a regulatory advisory group on a very important public health issue, but the doctors and patients have already run with this issue, that this chart based on IMS data said that back in middle of '09, there one million prescriptions a month for Yaz and it's now -- before the introduction of these compounds, it already fallen by 80%. So doctors and their patients, why I asked Dr. Lukes what was going on in her clinic and so forth, doctors and patients are running away from this.

They do not necessarily have epidemiological backgrounds, but they at least are aware that there are some studies and more of them are recent studies showing harm. So we now get to this question, if there was any evidence of any unique benefit at all, and it's not acne and it's not PMDD, it's not efficacy, if there were any, then it would be a much more difficult question to ask, because then we'd be faced with the idea of taking away something with unique benefit based on imperfect, but very suggestive data on risk.

So I guess my answer to the question is, it might have an impact, I would bet looking at the design of the proposed study, hopefully funded, it might have an impact. It might have an impact on increasing the risk. So I think that -- and I think other people said it in a more eloquent reason than I, that these various things could affect slightly down I would say equally or maybe more likely slightly up. And therefore, the decision about the benefit and risk doesn't need to depend on that.

We're being asked today, and I can't answer because I'm exempted from the vote on that question, we're being asked about the relative benefits and risks. And I think that the benefit question is simple. There is no unique benefit. And so if there appear to be unique risks, we need to go with it. Most drugs are not taken off the market because of randomized controlled trials. They're not even taken off the market for epi studies, because it appears that there's some unique risk and no unique benefit and I think that's what the case is here.

Julia Johnson: Thank you. Dr. Winterstein?

Almut Winterstein: Yeah, I'd like to echo what Dr. Hernandez-Diaz said. I think for each of these study design characteristics or measurement there are examples where a study has failed because one of these were not done right and the results were invalid. I think, however, it is very important to look at the impact of each of those biases in the studies at hand here and going through these exercise and try to estimate in what direction that bias would have had an impact, makes me believe that none of this can really explain why we see an elevated risk.

In terms of trying to get more information on this and doing further studies and looking at more confounders, again, we would need to have an idea what these confounders would be that are more present in younger, generally healthier women who are taking Yasmin and I'm not really totally sure I can see that. In terms of additional studies, one additional comment perhaps. I don't think a reanalysis of the existing studies is so helpful, just because the sample sizes are small and slicing and the data can only go to a certain extent. So any additional study would really need to be massive or include a pooled analysis of everything that we have seen now on a patient level, not only because the chance for random error will get larger, but also the impact of systematic error.

If you just have 50 cases, they are easily shuffled around from one exposure group to the other depending on how things are set. So the chance that systematic error can be generated by design becomes much, much higher. So if there were a subsequent study, it would suggest that it's massive, because I don't think that's in any other scenario, it would really add anything to what we have right now.

Julia Johnson: Dr. Kaboli?

Peter Kaboli: So to answer the question, I'd say, yes, that there could be channeling and other confounding, but from my reading of it before the meeting, and the discussion today, it seems like it would bias towards the null, in which case, I think if there was, we'd see a greater effect if we had all these other variables and all perfect information. And so the second part of question, are there other important confounding variables? Sure, there always are until we have the population and have data on every single patient so we don't have to use statistics, we have the actual real rates. But yes, we would love to have all that, but we don't, so we use statistics to try to come up with -- and do the best job we can.

Julia Johnson: Thank you. Dr. Morrato?

Elaine Morrato: Yes, thank you. I would agree with the other panelists who have talked about doing a more systematic analysis -- sensitivity an unmeasured confounding would be informative. There were two pieces -- a couple that I wanted to mention though. More specifically that as I look at the two studies, I'm still not struck with a good answer of understand who's enrolling in the European and these large registry type studies that have now expanded beyond Europe and I would like to see a more, a better understanding of how that might or might not be entering selection bias into the types of patients.

The other piece that I was really struck by in terms of the open public discussion was Dr. Gerstman's brief presentation of the impact of potential case definition of non-idiopathic and idiopathic and the impact that that might have on some of the differences that we see. So I would like to see a bit more evaluation of that. And then also the discussion around channeling bias focused largely on prescriptions or prescribing trends. And it's very difficult that the data that we're looking at today or what got published in 2007 was really data that was collected in 2001 to 2003, right when the product is getting launched.

That's a very different market environment than what we have now. So you can't really go back and try to understand, so what was your preferential prescribing or choices going back 10 years, which would be a challenge, I think if you were to try and do a survey with the existing Kaiser patients or Medicaid. But I think you could look back at the promotional marketing historical view of what was happening over the last decade and trying to understand how these products are being positioned through their advertising and from there, perhaps develop some hypothesis of how that might be leading to temporal changes in who's getting channeled to which drugs when.

And there are warnings that have occurred that are going to be influencing it and I understand that's a qualitative analysis, but that kind of work might then inform what variables or things you'd want to be collecting as we move forward. And then I'll just add also another vote for getting something around affluence or education. It was brought up in the open comment as well, and it was also brought up in one of the studies. I think it was the Netherlands study that found that affluence was inversely

related to VTE incidents and so that would be other supportive data why we would want to collect them.

Julia Johnson: Dr. Woods?

Mark Woods:: I don't have a lot to add, but I would second Dr. Morrato's comments about the impact of marketing and I think that cuts two ways. I think it's the impact of marketing to patients, but also the way these things are marketed to physicians.

Julia Johnson: Dr. Montgomery-Rice?

Valerie Montgomery Rice: I do believe that confounders matter and I am concerned that the data that we've seen, particularly in the FDA study that that was not accounted for; that we're going to be challenged to interpret the data as you start -- if you get to a second study I guess is what it would be where you would start to analyze that -- because I do believe it has been influenced by the marketing and the risk and benefits that have been perpetrated over the time about this study. I think even if you tried to a randomized controlled study now, looking at this you would have enrolled a different population of patients based on the risk analysis that has been so, I don't want to say well marketed, but it's definitely been out there.

As a person who spends of their time looking at issues in women's and looking at disparities, I am concerned that people don't feel it necessary to look at the risk profile that we ask every day before we prescribe somebody a pill. And we do take into consideration the socioeconomic status, whether or not they're going to be able to get the prescription filled. We look at their BMI. We look at whether they smoke. We get a family history. These are just some basic things that we do that help us determine which pill we're going to prescribe to the patient.

And yes, sometimes we end up not having many choices, but we clearly most of the time, document that we at least did that risk assessment and counselled the patient appropriately. So yes, I want to see other data collected on these confounding variables. And yes, I do believe there's been channeling, but I don't think we can do much about it, because I think we were heavily influenced by some of the marketing.

Julia Johnson: Dr. Orza?

Michele Orza: I would agree with everything that's been put forward and add three small things. I do think that there's a lot more that can be done to analyze the existing data in the spirit of a formal synthesis with some modeling of these confounders and some sensitivity analyses to try to tease these out. I think in thinking about what you might like to do additionally, I think we need to kind of flip it around and say, and it relates to questions we're going to answer later, but what is it really that we still feel we need to know.

Is it as Dr. Wolfe said that there's no additional benefit here, so any increased amount of risk, zero is our threshold. Is it two times as somebody in the public comment period suggested? What exactly is our threshold for making the decision or changing our mind? And then I would subject that to a value of information analysis to see is it really -- what will it take to get that information that will change our mind and what is the cost of that and is it worth it.

And then lastly, I continue to be the most confused and troubled about the so-called channeling bias, because I can't kind of tease out the logic there. Presumably, women

would be channeled based on the additional benefits, the acne, and the PMDD, and those would somehow have to be related to an increased risk of VTE, and if that were true then they would not be candidates for these drugs. And so that would kind of cancel their benefit. When I follow that logic train, I get -- it works against the drug.

Julia Johnson: Yes sir.

Richard Bockman: Thank you. I am not an epidemiologist and with respect to these various studies, I would just say that it's a case of cognitive dissidence. We're dealing with a real adverse clinical outcome in terms of VTEs and pulmonary emboli and we're looking at studies that are basically being done at 30,000 feet to see what's going on. And then we spend a lot of time talking about confounders, which I always find funny, because they're basically the smudges and the shadows. What we really need to do is try to understand what actually is in some ways causative or could be an explanation.

The confounders are infinite. I mean we haven't even talked about the genetic compositions that people bring to these pills. We don't talk about their neutriceuticals that they're ingesting left and right. I mean it's extraordinary what our patients are on and I think it probably makes a huge difference whether you're on a statin, an aspirin like drug or whatever. Even calcium has recently been fingered as a potential cardiovascular risk factor, calcium ingestion. So I think one thing must absolutely be certain with these studies and that is that there has to be absolute full transparency of the records of these patients.

And this is going to become even more impossible as time goes on if we follow the HIPPA privacy rules are being imposed upon our studies. And the last thing is that I think channeling -- I'm actually trying to answer some of questions, channeling, I think is a dead issue. I mean if anything, based on the data that Dr. Wolfe has shown us, if it's true, the feet are running in the other direction. So I mean we are undermining channeling, if it did occur. So channeling is only relevant if we're going to be constantly fighting over these past studies and debating the past studies. I think it's going to be a non-issue if we go forward.

Julia Johnson: Thank you, Dr. Bockman. Dr. Hoeger?

Kathleen Hoeger: Yes, so I'll make my comments brief, because I think all of the comments have really summed up how I felt. However, I do believe that as a clinician prescribing contraceptives, we follow the WHO criteria and we do look at confounders and we do advise risk based on confounders and I think we should include these in the study. So clearly all of the comments previously, these are important to look at. I think we ought to look also not just at the neutriceuticals, but also many of the activities and lifestyle efforts.

PCOS, particularly in the FDA study, I think we have a real lack there, because we certainly know that the population at risk is much higher than what was reported. So what we're pulling out of that data has to be re-evaluated for that. But having said, I think that these are modest contributors as has been pointed out, and I think in some cases would bias in the null direction and I feel these have been looked at appropriately.

Julia Johnson: Thank you very much. Dr. Kittelson?

John Kittelson: Thanks. Yeah, so I would like to frame the logic, our thoughts in terms of what would we do if we had perfect information? We would probably call this a non-inferiority study on VTE, because women need choice and there might be advantages to this compound over some others. And so we would have randomization as a centerpiece because we know that there are confounders if we don't have it. And the closest we can get to that is what we should be striving for.

So I don't think we'll ever to be able to adjust for confounding. In classic epidemiology there are two ways, right? Study design, you fix it by study design and fix it with statistics and statistics never work, in spite of my background. So study design is really where we need to go and therefore, whatever we could do in perhaps a second stage of the FDA study to get as close as possible to randomization is going to be, I think, the key and to try to think about what that means. I think propensity scoring is perhaps one of the best things we could think about. I don't know how feasible it is there.

The other thing that we worry about carefully in non-inferiority trials is what exactly are the treatments that we're going with and do they reflect standard of care. So out of necessity and I think for good reason, you've looked at first time users in the current studies, but these contraceptives are used in many other settings and the risks across all of those groups or not. And you would want to, as far as you can, reflect how the contraceptives are going to be used. And so first time, all time, kinds of users. And then time trends. And we clearly have time trends, and somehow those would have to be accounted for with basic randomization we would get the balance and it would carry forward in time, but we don't have that luxury here.

The other thing is what is the target population here? Is it young and old? Is it smokers? If these third generation are considered to be less risky, if that would a consideration, then perhaps you get higher risk individuals coming on to these studies. So I don't believe we know the direction of bias. I think there are huge confounders that are left out there that will be unmeasured and so the best we can do is a next stage of an FDA study, to think very carefully about what would closely reflect a clinical trials and try to remove those as much as we can through design rather than through adjustment.

Julia Johnson: Thank you. Dr. Gilliam?

Melissa Gilliam: So I there are two questions. What's the quality of the current data and what would we like to see in a future trial? I think the ideal current data would have been a non-sponsor funded cohort study that was done in the United States and we clearly don't have that. And I think there are a number of reasons why all of the data that we're looking at are problematic and have some issues. I don't think that most providers are providing oral contraceptive to hypertensive smokers. So I don't -- while I think it would nice to know that for the FDA, I don't think that's going to be this huge population, but I think clearly when we think about things like channeling, it's a shifting landscape.

In 2001, it was a huge market share. Probably everybody was trying the new pill, except for people who couldn't afford to buy name brand products. And then later on we had, people walking away from the pill. So it's shifting landscape and I think the way that we provide changes -- right now, Yasmin, I would only provide to patients who have PCOS. And sometimes I don't even provide it in that case. So very different from maybe what I would have done five years ago. So I think going forward, other

things we have to take into account. One, our demographic variables. I want to understand why and who might be at risk for a DVT. And so those are also questions about mechanism. The other is adherence.

I think we've talked about whether people are filling their prescription, but as someone who studies adherence, people don't take pills and it's incredibly hard to measure whether someone is actually taking a pill. So I think we have to have another grain of skepticism as we look at studies. And obviously, it's not necessarily a source of bias, but I do think -- or a bias towards showing a high-risk of DVT, but I do think we have to look at the potentially different adherence within different studies. And again, I think when we're looking at what people are doing in real life based on large databases, most likely the adherence is very poor.

Julia Johnson: Dr. Clark?

Bart Clarke: I agree with pretty much everything that's been said. I think because of confounders and the differences between the studies, it makes it very hard to say for sure what's really going on. There is a trend and I'd say I'd be concerned if there is an increased risk, but it's probably a modest increase in absolute risk. I think to go forward, looking at these studies and trying to do further analysis I don't think is going to answer really the questions and as has been said by Dr. Kittelson, I think that trying to make the upcoming FDA study as best as it can be, to try to get an answer to some of these questions is the best way to get some knowledge that will actually clarify these.

There's certainly many important confounding variables, and like I say, there's so many, it's very difficult to control for all of them, but at least the big things and I think BMI and smoking would be two obvious things that should be addressed if we're going to move forward in this area.

Julia Johnson: Thank you. Ms. Aronson?

Diane Aronson: In the FDA background information, Section 5, future activities, the FDA finding that studies indicated a potential increase of VTE associated with the use of the drugs. They recommend further study and on page 43, they lay out a number of issues. And so, I would support those along with others that -- so I won't repeat. I agree with what's been said.

Julia Johnson: Thank you. Dr. Stovall?

Dale Stovall: Yes. I think this problem is about as difficult as the clotting cascade itself. Many of us have memorized and forgotten that many times. And you know I think without all the protectors in use that keep us from clotting, our intravascular space from clotting every day, every moment, antithrombin probably primarily, that that would be happening. So all of these -- sure, all these variables make a big difference. They make the difference. And there's some threshold at which you cross where a clot occurs, it's clinically significant.

But getting to what that threshold is and whether all these variables are synergistic, additive, et cetera, is going to take a long, long time. Especially in (inaudible) event, which is intravascular event. So I think, yes, they all make a difference, but it's going to take quite a while before we get to that point where we know you can calculate someone's risk and say, okay, you're approaching that threshold and therefore you're

not a candidate. So I wish I could give something better than that outlook, but I think that's where we are.

Julia Johnson: Thank you. Dr. Hillard?

Paula Hillard: So I'm concerned that there are some very important variables as has been mentioned all around the table that have not been adequately assessed -- BMI, obesity, diagnosis of PCOS which is clearly under diagnosed in general practice and the numbers we see for the studies are very, very low. I think this makes it extraordinarily difficult for us to determine any magnitude of increased risk, if there is an increased risk. And so I think that's really the challenge that everyone is expressing.

As a clinician, I'm absolutely sure that in the past, channeling has absolutely occurred for some women who are at increased risk of venous thromboembolic phenomenon. Women who have irregular periods, have acne, who may have some hirsutism. Basically, women who have PCOS who have not been diagnosed as having PCOS are very frequently put on the pill, and that is especially true for adolescents and young women. And these are the patients that clinicians are saying that Yasmin or Yaz is a perfect pill for and have been saying this in the past.

And these are the patients who are asking for these pills, because the patients themselves perceive that there are some benefit. So I think that has occurred in the past and I think it still an impression among clinicians that there may be some unique benefits for this population. We're seeing numbers declining, as we saw with the graph today, among patients. But I think that among clinicians there is still the impression that these pills have unique benefits and I think that remains to be proved comparing to other pills, but it's certainly the impression and it is plausible, and given the drospirenone and its analogy to spironolactone.

One other issue to think about just briefly and as we think about going forward is the issue of screening on the basis of family history and it hasn't -- clearly that's very important, but I would suggest that young women, adolescents and young women in particular, are unaware of their family history of venous thromboembolic phenomenon or other cardiovascular risks. And I think one thing that could come forward is increasing education of the public about the importance of family history and this is something that might be included in labeling as well.

Julia Johnson: Thank you very much. Dr. Hewitt?

Geri Hewitt: My comments too echo a lot of the things that have been said around the table. Overall, my impression is that the information we have is somewhat conflicting and that overall there may be a slight increased relative risk in the oral contraceptive pills that contain drospirenone, but that overall that these pills in terms of absolute risk, the risk is very small in terms of VTE in the patient populations that they're being used for. And I do appreciate the comments about channeling and that's a dynamic landscape.

As someone who's a clinician in a very busy practice site with pediatricians, family practice doctors and lots of phone calls coming in, I can't tell you how many times, particularly three to five years ago, people said this is the perfect pill for this. Right. And that not only was marketing to patients, but as well as marketing to clinicians. So you know and all the patients that were started on Yaz or drospirenone-containing products by a PCP or pediatrician, that I think that that feels very real to me and it's hard for me to dismiss that.

But overall, I think that there may be a trend in increased relative risk, but the absolute risk is still low.

Julia Johnson: Thank you. And Dr. Espey?

Eve Espey: Yes, I agree with the other panelists, and I do particularly agree with Dr. Montgomery-Rice about the importance of confounders. I mean I think that those -- that's really not the background noise. It's so much of how we decide whether to put somebody on a pill at all, which pill to put them on, how long to put them on for, and those things do include I think important things that haven't been looked at it in all these studies, including BMI, smoking, race ethnicity, poverty, insurance status, personal history, family history, and then GYN diagnoses -- PCOS, but other GYN diagnoses as well.

And I do think fortunately as well that if there is an increased risk, it is modest and it is small compared to the risk with pregnancy. And when I see this handout that Dr. Wolfe passed around, what I worry about is what happened to those 800,000 women and did they get a prescription for something else? Did they -- as concerning as the risk for VTE is, I think that it's always important to keep in perspective the risk of pregnancy and what happens when these big shifts occur because of panics around study findings like this.

Julia Johnson: Okay. So I've gotten information for discussion question number one. I've also gotten what I believe to be sufficient information to put together a consensus for number two and number three. Let me go ahead though and start off with discussion number one and I am open to any significant concerns in regards to this.

But briefly that indeed all of these studies have significant strengths and weaknesses. And that indeed it becomes confusing when we're comparing these studies, because of studies, especially the FDA study, and Ingenix which appear very similar to each other to find conflicting results. We are, in addition, very concerned about the fact that we have not seen all the confounders. And indeed we do need a systematic analysis, and I wrote down a list of all the issues that were raised including BMI, smoking, exercise, family history, PCOS, time trends, new users, socioeconomic status, ethnicity, other medications including over-the-counters, issues related to aging, marketing, and GYN diagnoses.

I think that anything that can be done to look at that data, especially with the two U.S. studies and being able to look at those confounders and asking both the sponsor and the FDA to look at those would be absolutely critical. And then a third issue that I think came forward fairly clearly is that the committee believes that a new study is needed to continue to look at the FDA data, that we can have validation of the outpatient data more consistently. That indeed we can have more confounding variables considered. I think that there is great possibility to be able to really answer this question and that's our great hope for the future and I appreciate Dr. Kittelson's and others ideas, that this indeed is our best hope for the answer to these questions.

So comments in regards to that?

Valerie Montgomery Rice: That was pretty good.

Julia Johnson: Thanks.

Unidentified Participant: Yes, but I (inaudible) add something to it. Just mechanism, we haven't seen a lot of discussion of mechanism, except for a few mentions here and there. But in looking at and designing the future studies to look at groups that ought to -- to dose response kinds of things, exposures, highly sensitive groups, do we see things that are biological plausibility at all. So in all of fact, I would at least underpin it with biological plausibility. Thank you.

Unidentified Participant: And just to plug in, we'd like to have it analyzed according to plausibility, rather than a computer.

Julia Johnson: Thank you very much. Let's go to question two and I'll give you my -- or discussion point two, if we could pull that up. Based on your evaluation of the strengths and weaknesses of epidemiologic studies, do you believe that some of the studies or findings should be given greater weight than others? What I heard from the committee was that all of these studies had their strengths and limitations. That indeed there are concerns with all of these studies that could be raised. And therefore, that they all should be considered, but indeed we need to obtain more data from those studies as possible. Again, I would say especially the two U.S. studies. So other comments in regards to this? Dr. Kaboli?

Peter Kaboli: Just one comment to that. I mean I guess really the question is we can always do more studies. If we have unlimited time and unlimited money, we can do more studies. It keeps me busy all the time. The problem is at what point do we stop and say, we have enough information. And I think that's where we are with this is that do we need beyond a shadow of a doubt that there is risk here, when I cannot see there's any benefit, so -- or do we want a reasonable doubt?

Julia Johnson: Thank you very much. Dr. Espey?

Eve Espey: I think it probably is worth a study and I'm not sure if it should just be drospirenone. I mean I wonder if those third generation contraceptives could be thrown in there as well, because we're not talking about that, but the same concerns relate to the third generation. We don't talk about those anymore, but a lot of women are still using those contraceptives. In terms of the public health impact, it's huge. I mean there's just a huge proportion of American women that use oral contraceptives. So although it would need to be a massive study, as I think was discussed before, it does seem like that would be worth it.

And the other thing is I think that one of the big reasons we have so much skepticism about the studies that showed no increased risk is because they were funded by the sponsor. And as somebody in the public brought up, there is this willingness to please of studies that are funded by sponsors and it would seem important that be a truly independent study.

Julia Johnson: Dr. Raymond?

Elizabeth Raymond: Yeah, I wanted to offer a different perspective. I am skeptical that more studies or more analyses of the already collected data will settle these questions. I think at some point we do have to stop and make the best decision we can based on the limited data and I think we're at that point. But in addition to that, I think money and time are finite and precious and VTE, as we've heard today, is a devastating event, but the fact is fortunately it's very rare. And I think in the big picture, other issues related to oral

contraceptive pills may have more of an effect on women's health than VTE, including issues like access and compliance.

Oral contraceptives that don't contain any estrogen at all, we could explore the -- how to increase use of these kinds of methods that would actually, potentially, really decrease VTE risk. And I think the FDA has a role to play in this and I think it's worth considering what the big picture and what FDA could do with its money.

Julia Johnson: Dr. Montgomery-Rice? No? Dr. Schisterman:

Enrique Schisterman: Yes, so I agree with Dr. Raymond that asking for more studies is like asking Wall Street if they want the Dow Jones index will go up. Of course we want more data. But I think that there is something that I want to emphasize that has been missed. That there is something that can be done better with the data we have right now. That it allows us to answer questions that we are all in doubt that with different methods, we could be addressing. Using a meta-analysis, using sensitivity methods that have not been summarized by you. So I wonder that -- I want to make a strong case that more can be done with the data available by the sponsor's studies and by the FDA studies.

Julia Johnson: Thank you very much. Dr. Monroe, you had a comment?

Scott Monroe: Yes. I just wondered if it would be possible for us to perhaps move onto the two voting questions, which are sort of questions that reflect what we will be doing in the short term. And then with whatever time is left, as we had really structured it, more general questions again of what we can do with a longer term perspective. My only concern is that it's getting close to 5:00 and certainly if the committee members are willing to stay over and continue to discuss it, we want to hear everything we can. But I just want to ensure that we get to the two voting questions.

Julia Johnson: I think your suggestion is excellent. Let's go ahead. We will come back to number three. I think it's an important question. Let's come back to that. But let's come to the voting areas next, because that is really why FDA has us here. So let's move on to number four.

Do you believe that in the general population of women who desire contraceptives, the benefits of DRSP containing oral contraceptives for prevention of pregnancy outweighs their risk? So will now, let's start on the side with Dr. Espey and -- I'm sorry. Thank you for helping me with that. So we have on our panels both yes and no, and if I would ask for a vote of yes or no from the committee. You must push the button twice please.

So as we're voting, I'll thank the committee again for their patience with me in regards to this. After we see what our vote is, if the predominance is not, then we will ask about subpopulation. I apologize again; the vote did not go through. Please press the yes or no again, while it's blinking. It will not blinking.

So our total vote is 15 yes, 11 no in answer to question four. Since we had a predominance of yes votes, there will not be the question of a subpopulation for whom the risk benefit would be favorable.

Now we're going to move on to the next question and then we will come back from there for discussion of number three. This vote is, do you believe the current DRSP

labels adequately reflect the risk benefit profile for this product? Please press yes or no.

Scott Monroe: Excuse me, before we vote --

Julia Johnson: I'm sorry. Go ahead.

Unidentified Participant: Yes, we're supposed to I believe have each person who voted say why they said yes or no.

Julia Johnson: I apologize, again. Okay. So Dr. Espey, we are going to begin with you in your vote and why.

Eve Espey: I voted yes, because I think the elevation in risk, it if exists, is modest and it's outweighed by the risk of pregnancy and I think having more choices is appropriate.

Unidentified Participant: I would echo that for similar reasons. I voted yes if the absolute risk was very low and the risk associated with pregnancy was far greater.

Unidentified Participant: I voted yes. Ditto.

Unidentified Participant: And I voted no, because I don't think in patients with thrombophilias and several other populations that it would be appropriate.

Diane Aronson: I voted no. This is Aronson. Because of the confusion regarding studies and the differences and the results of the FDA Phase I.

Julia Johnson: Please state your name for the record also when you give your vote. Thank you.

Bart Clarke: Clarke, yes, because there overall benefit still outweighs the risks, even though I think there's a small increase in risk, modest increase in absolute risk.

Melissa Gilliam: Gilliam. I voted yes. I took a no vote to mean that it should be off the market and I didn't think that was right, so I voted yes.

Scott Monroe: Excuse me. I'm sorry to interrupt and be rude. For those folks who voted no, it would be helpful to hear if they have subpopulation -- I think we heard that from Dr. Stovall. He suggested certain folks that he thought would not be good candidates. I think that's how I interpreted it. So for those folks that said no, if they could have the opportunity to identify a subpopulation, since we are going around. Would that be acceptable to --

Julia Johnson: That's acceptable.

Scott Monroe: Thank you.

Julia Johnson: Any other comment, Dr. Stovall?

Dale Stovall: No, and that was my point.

Julia Johnson: Yes.

John Kittelson: John Kittelson. I voted yes. I voted yes, because I don't think we have a good handle on what the risk is yet. The best studies in my mind are showing no substantial elevation of risk. Thanks.

Kathleen Hoeger: Kathleen Hoeger. I voted yes. Again, prevention of pregnancy is much stronger indication in this situation. The moderate risk may (inaudible) there by the data, but I believe the choice that women have terms of variable pills is important.

Richard Bockman: Bockman. I voted no, because I don't -- I didn't see clear evidence that the benefits outweighed the risks and I would think that subpopulations who potentially could be at increased risk was hematologic disorders, strong family history, smoking, obesity, et cetera, et cetera, probably should be not using this drug.

Michele Orza: Orza. I voted no because I could not perceive any additional benefits, only with these drugs and so any additional risk, even small, and I don't think the risk is potentially as small as some people are suggesting. Even only a 50% increase would represent thousands of unnecessary VTEs. I think that there are plenty of options already and I don't see because they don't have additional benefits, what these add to the options. In terms of a potential subpopulation, I guess it would be only women who can't take any other pill, but really want to be on a pill. That's the only one I could see making any sense.

Julia Johnson: Johnson. I voted yes. And the reason for that is that I don't think the data is sufficient with the current studies to be able to say that there is a risk. However, I am significantly concerned regarding the most recent FDA study. I think that the FDA needs to move forward with this. I would like to see comparison with other U.S. study. I think that's absolutely critical. I do not think there is one advantage for this pill over any other for use for women. If indeed there is truly an increased risk, then I would vote differently.

Valerie Montgomery Rice: Montgomery-Rice. I voted yes, because I believe that the risk, if present, is a small absolute risk. But when you compare to the risks associated with an unintended pregnancy, I think that is greater. And I believe that women should always have a choice and so that they can make decisions on how they want to provide prevention of pregnancy.

Mark Woods: Woods. I voted no. And basically I can see no real group of patients that this benefited over existing alternatives. And so without any clear benefit given modest, but potentially catastrophic risk, I voted no and I would agree with the risk factors that were previously stated.

Elaine Morrato: This is Elaine Morrato and I voted yes for many of the same reasons others have voted yes. That although the safety findings are contradictory and disturbing, it does appear that if there is an increased risk, the absolute incident rate is still very rare. It appears within the general range of currently available products based on the class labeling that we were shown, and that the risks remain significantly less than the risk in pregnancy and postpartum period. I also found the neutral mortality data from the FDA study to be reassuring.

However, if the standard is to make a comparative, which we -- I just compared it in absolute sense, I would agree that I didn't see any benefit of the product that's well demonstrated for Yasmin, perhaps for Yaz. And so if the regulatory standard would be that you'd have to demonstrate a comparative benefit, then I would vote no.

Peter Kaboli: Peter Kaboli. I voted no, because when weighing risks and benefits for patients, I have to see that there's some benefit. So the number needed to treat to have some benefit in this case, in my opinion, would be an infinite number, because there is no clear benefit. Therefore, the number needed to harm, regardless of how small that is, is all harm with no benefit. And I wouldn't recommend this to my patients and I wouldn't have my daughter take it. So I voted no.

Almut Winterstein: Almut Winterstein. I voted no. I struggled with the way the question was phrased, because risk benefits just (inaudible) contraceptive, of course there is a benefit because it is an effective contraceptive agent. But the (inaudible) really the comparative effectiveness and safety here, so for the reasons already stated before, there is no demonstrated superiority with respect to any feature. There are potentially safer alternatives available. So I just thought first do no harm and unless we can a study that proves that drug is as safe as any other contraceptive on the market, I would stay with my no vote.

Sonia Hernandez-Diaz: Sonia Hernandez-Diaz. I voted no because even I agree that the absolute risk is going to be small, until we rule out the potential modest increased risk, since we don't see clear evidence of benefit compared to other forms of contraception, I think the risk might be greater than the benefit in this case.

Maria Suarez-Almazor: This Maria Suarez-Almazor. I also vote no. The question was to compare benefits and risks and I also took the approach of comparative effectiveness. And with respect to benefits, there's no clear evidence of benefits over the many other forms of birth control and oral contraceptives. And with respect to the risks, I was a little disturbed by the fact that every single study that was no funded by industry found an increased risk and it was only the studies by industry that showed no risk, and that was somewhat disturbing for me.

Unidentified Participant: I voted yes, because the data before us I thought was --

Julia Johnson: Please state your name, Dr. Wild.

Robert Wild: I'm sorry. Robert Wild. I voted yes because the data before us was conflicting and I don't think that's a clear answer from what we saw. I don't think the data was -- we were asked to analyze comparative data. I didn't see that that was our charge. I felt like compared to the alternative of getting pregnant, clearly it's a benefit. And then I felt that as clinicians, we need to make judgments and we have that choice and don't want to take that away from patients or physicians.

Naomi Tepper: Naomi Tepper and I voted yes because I also interpreted it that if a no vote would perhaps mean that it was pulled from the market. And however, I may feel about the marketing that's done, I felt that if there were women who believed that this pill would be benefit to them and they would take it reliably and consistently that that had to be taken into consideration given the risks of unintended pregnancy.

Jacqueline Gardner: Gardner. I don't usually vote against choices, but this time I did and the reason is because on the benefit side, I didn't see any improved benefit over the existing available choices and there are so many of them, I believe that as far as oral contraceptives are concerned, women could find alternatives. I don't see that the alternative to this product is necessarily unintended pregnancy. That's not the balance, but rather other safer alternatives. And I, too, believe that when all of the studies are

analyzed adequately that we may find that the risk is even higher and that translates to a large number of women in public health terms.

Sean Hennessey: Sean Hennessey. I voted yes. It was a difficult vote. I think that the drug ought to be rarely used and probably not first line. On the other hand, I think that the magnitude of probable risk is such that it doesn't make it an unreasonable choice for women who derive benefit from this oral contraceptive compared with others. I don't think there are data that is worse in terms of safety than desogestrel, which is on the market. And I think that it's possible that future studies will show comparative benefit in terms of PMDD and acne versus other agents. But I'm agnostic as to whether those benefits exist right now.

Elizabeth Raymond: Elizabeth Raymond. I voted yes. Oral contraceptives prevent pregnancy and many other serious health conditions and these effects clearly outweigh the relatively low risk of venous thromboembolism.

Enrique Schisterman: Enrique Schisterman. I voted no because there are plenty of other alternatives that do not show any increased risk. One of the main things is do not harm. And even a small excess of risk is no -- we shouldn't take that lightly.

Anne Burke: Anne Burke. I voted yes. I don't think I was expecting it to be more effective than other pills on the market, and while I acknowledge that there does seem to be a moderate increased risk, it's still lower than the risks of pregnancy. And like some other folks who have spoken, a no vote sounded like it would be -- to take the product off the market. I'm not quite sure that's necessary at this point.

Julia Johnson: I would like to thank the committee for your votes and your comments. I believe we will be answering three and six just with our ongoing discussion, so we're going to conclude this meeting with a vote on five. I'm going to read it to you. Do you believe the current drospirenone label adequately reflects the risk benefit profile for this product? If everyone would vote, please.

Unidentified Participant: Before we do that, could we see the label for desogestrel and the label for drospirenone?

Julia Johnson: Thank you for that reminder. Could we bring those forward?

Unidentified Participant: Is this just related to VTEs or is it all serious adverse events? I mean it just says regarding risk.

Scott Monroe: We would like the discussion to focus on what today's topic was, which was related to venous and arterial thrombotic risks.

Unidentified Participant: Could I ask a question too? There is the physician part of it and the patient part of it. Are we commenting on both, or just the physician part?

Scott Monroe: You can comment on both. I think the patient part will reflect whatever guidance you give us in terms of the physician part, but certainly anything you want to help us with will be appreciated.

Unidentified Participant: Just one other point. Just from having looked at the -- not the Yasmin one, but the other three that are in that sort of patient friendly language, there's much less detail for the patient part than there is for the physician part.

Scott Monroe: That's a comment that you've already conveyed and I appreciate that. But no, again, the patient part should mirror what we put in physician in less detail, as you've indicated, but yet convey the important message that we have in physician labelling.

Julia Johnson: While we're waiting for a moment for these to come up, any other comments in regards to labelling? Yes, Dr. Gardner?

Jacqueline Gardner: We've focused on the VTE risk today, but as I was perusing these labels, I'd also like to point out that just the general label is really quite old and we're citing data on mortality risk in comparison with oral contraceptives and versus pregnancy, versus the general public, from a study that was done in 1983. And there's another one having to do with maybe thrombophlebitic risk -- cardiovascular risks, that came from a study whose date is not given, but it was Valerie Berrell (ph) was the one of the authors. And I can't even find it in PubMed and that was probably a very long time ago too. So I would suggest that not only what we're dealing with right now be looked at for these specific products, but I think it's time to update our general package insert to reflect products that we have now.

Julia Johnson: So we have in front of us the Yaz current information from April 2010.

Unidentified Participant: Why do we have Yaz?

Julia Johnson: Can we get Yasmin? This has the newer language?

Scott Monroe: This portion of the language --

Julia Johnson: Will be on Yasmin?

Scott Monroe: Yes. Yasmin -- we'd make no changes, would look like this in the very future, but I -- we waiting for your guidance and then they will both be -- everything will be harmonized.

Julia Johnson: So this is the comparison?

Scott Monroe: I mean the key piece related to EURAS, Ingenix and the two studies from Europe from 2009, I believe the wording is identical or close to identical, other than the Yasmin label says the studies were a comparison against -- I'm sorry -- yes, Yasmin says the studies were a comparison against Yasmin as indeed was the case, where the Yaz label says that it was a different drospirenone-containing oral contraceptive and just makes that fine distinction that we've done here. But in terms of, I believe, describing the outcomes of the studies, are they not identical, the folks from Bayer, please.

Leo Plouffe: So all this language is currently in all of our labels. So Yasmin, Yaz, Beyaz and Safyral, that's specific language. The difference between Yasmin and the other labels is all the other labels have been converted to DPLR format and that encompasses, as Dr. Soule has already pointed out, the language for example around the frequency of event of VTE and so on. But the language about the specific studies is the same across all labels and that's the language that's in there right now.

Julia Johnson: Dr. Kaboli?

Peter Kaboli: Yeah, I think an important point here is that when you look at the literature about patient decision making and health literacy and health numeracy and the ability to interpret these labels, is incredibly difficult. This is incredibly difficult for physicians to read and understand. So if we think that patients are reading these and understanding them and making informed decisions, we are delusional.

Julia Johnson: Just because I want to be respectful, for anyone who may need to leave, we'll take several other comments, we'll vote, we'll let anyone who needs to leave, get their vote first, and then we'll go around the room. So Dr. Morrato?

Elaine Morrato: So can we just see the wording again on that class labeling and then also what's in the patient package insert? Just so that we -- that was actually my point. There's a separate part that's for patients that's much, much simpler than this, but also really does not include any of this comparative sort of -- is there a patient part here? Do we have that?

Julia Johnson: We do not have that.

Valerie Montgomery Rice: But we do have the class labeling that you showed us.

Julia Johnson: (Inaudible) show that class label again. The Yaz class label that the Yasmin's soon to become.

Leo Plouffe: Yeah, it's only a portion. And unfortunately we were not planning to show the whole label as slides. We can put up what we've already shown.

Unidentified Participant: You showed it earlier though.

Julia Johnson: Wait, one moment before we go to that. We'll come back to you. Okay. This was the class labeling.

Scott Monroe: May I make a suggestion that if you focus your attention on what's in the physician label and if you don't deem it to be adequate, and what your suggested changes would be because we do ask you specific questions whether -- if you feel that it doesn't fully reflect the current data, and I'll acknowledge right now we specifically did not update the label in September or October because we were waiting to get your input.

And whether you think that the best way to convey the additional information from the studies that were made available in 2011, which are three studies: the two non-FDA funded studies and the FDA funded study. Whether the approach, which we have done in the past, and several regulatory agencies have done, in terms of just basically listing findings from all the studies and letting the reader make his or her own conclusion, I'm talking about the physician piece now, or whether you feel that this information should be consolidated into an approach which was done with the EMA where they make a summary conclusion based on the totality of the data is I think the question that we're posing to you today if you feel that the label does need to be revised.

And I think for just expediency and the limitation here, if we just focus on the physician part, which is shown to you I believe here for Yasmin where it's -- the wording again is the same for Yaz and all drospirenone products will carry if not identical, virtually identical language. And we would like your thoughts as to what you feel that language should be. Does that help to explain, Dr. Johnson or have I further muddied the charge to the committee?

Julia Johnson: I think that's a fairly big charge but we'll do the best with it that we can. Let us go ahead and go back to the previous slide. I know it's difficult to read but if we can go back to the previous slide. Any other questions that are critical?

Unidentified Participant: So are we going to see desogestrel?

Julia Johnson: They do not have it.

Unidentified Participant: Does the label for desogestrel make a conclusion about whether there's an increased risk for or it or does it say on the one hand and then on the other?

Unidentified Participant: No, it just mentions the fact that some studies have shown it, other studies haven't. So it doesn't make a firm conclusion about definitely a higher risk.

Julia Johnson: Okay, so let us look at this and say whether or not we think this needs to be adjusted. So again, the question, and I'll just read it to you, we'll leave this up. Do you believe the current DRSP labels adequately reflect the risk benefit profile for this product? Kindly vote. Vote now please. One more pressing, please. So anyone who does need to leave, who needs to catch a plane, if you want to go first. Dr. Hillard, I don't know if you need to get going.

Paula Hillard: So I voted no. And I believe that the current labeling summarizes some of the studies that we now have available. I believe it should summarize the additional studies.

Julia Johnson: Thank you very much. You may go. Now let us begin now with Dr. Burke?

Anne Burke: I voted no, in part because I generally have an issue with these labels. I think they're really hard to read for providers and patients. But I also think, you know on the last question I voted yes, even with a possible increased risk of VTE, I think this method should still be available. But I also think that results like we're hearing today need to be fairly transparent. So even if it's just a possible increased risk, I think we need to say that and I think we need to say it fairly concisely without a lot of epidemiological disclaimers so that women, and providers too, can really make informed decisions.

Julia Johnson: Thank you.

Enrique Schisterman: I voted no because -- it's my time? Yeah. Yeah, so I voted no because it was weighted towards the positive findings (inaudible) negative findings. The results were questioned more on the case-control study and the retrospective cohort study than the positive. So not balanced at all.

Julia Johnson: Thank you. So just to note, this is 24 no, 5 yes. And next, Dr. Raymond?

Elizabeth Raymond: I voted no. I was a little bit confused exactly what we were voting on, to be frank. But I think we were voting on the slide that had the two different sections to it, which, as far as I could determine, included some studies and not others. And it seems to me that regardless of anything else, that doesn't make very much sense. As to what the label should say, I agree with my colleagues here who pointed out the complexity of labels and that they should be simpler, both the patient part and the physician part. Most physicians aren't epidemiologists and these are complicated issues. And I think, if the FDA is going to do further research, further research into that, it might be something that would be worth doing.

I don't think, in response to Dr. Monroe's question, that a single summary statement should be on the label because we don't really know what the single summary should say. Whether each study should be described on the label as it is, I'm not sure either. Because, as I mentioned, labels are too long and maybe not the place to be putting a review of the literature. I think further, serious thought needs to go into how to write labels.

Julia Johnson: Thank you. Dr. Hennessey?

Sean Hennessey: So I was voting on the question, should the label unequivocally state whether or not there is an increased risk. So I think that the label needs to communicate some uncertainty. I'm not sure of the best way to do that because I think there's more certainty about desogestrel than there is about drospirenone. Since there's uncertainty expressed in the desogestrel label I'm comfortable with there being uncertainty expressed for the drospirenone label.

Jacqueline Gardner: Gardner. I voted no for similar reasons. And I think the FDA has a Risk Communication Advisory Committee and it also has risk communication specialists on the (inaudible) and can get some help here. But generally trending toward more tabular presentations where people can compare studies in a table and what the findings were so that they can see for themselves whether there was disagreement. We don't need all that wordy interpretation. And also I think someone mentioned that this language goes heavily toward the positive side and is dismissive of the conflicting results and I think that needs to be corrected.

Naomi Tepper: Tepper, and I voted no for the reasons that really have already been stated. I think the label needs to include all the studies and should be much clearer for physicians to understand. I think more of a sort of a summary statement would be really helpful.

Bob Wild: Wild. I voted no because I felt like the message needs to be updated and simplified.

Maria Suarez-Almazor: Suarez-Almazor. I voted no for the same reasons that have been stated.

Sonia Hernandez-Diaz: Sonia Hernandez-Diaz. I voted no because I think the label can be simplified for the clinicians. We spent here the whole day and we still didn't figure it out and explain the difference among the studies. So I agree that perhaps having these references or the discussion or the report from the FDA available on a website so that clinicians that are interested in reading more can go there and read more.

But in the label, I will summarize the conflicting evidence acknowledging that there is conflicting evidence. And also I think it is very helpful for the patients, if we do that, to put the results into context and write something along the lines of the baseline risk is the order of five every 10,000 and conflicting results but current studies say yes that perhaps the risk, if you use these oral contraceptives, can go up to 10 every 10,000, something along those lines to put the risk into context I think would be useful too.

Almut Winterstein: Almut Winterstein. I voted no for the exact same reason that Dr. Hernandez-Diaz just said, so no addition.

Peter Kaboli: Peter Kaboli. I voted no for the same reasons.

Elaine Morrato: Elaine Morrato. I also voted no. Just wanted to add a few points. I noticed in the class labeling we do things like quote rates of 3 to 10 out of 10,000. You know, when you look at the Yasmin studies it's a paragraph form. So as many have said, I think tabular, visual would be more useful, helps to compare. Might we think about doing the equivalent for VTE the way they have with the efficacy table, or that graphical thing where it's sort of a sliding scale based on the contraceptive efficacy, which is similar to what was presented and showing sort of that three people versus nine people kinds of things.

I think that whatever's communicated needs to be consistent between patient and physicians. And it sounds like simple for both would be very useful given the complexity of the data. I would agree that the Risk Communication Advisory Committee, this might be something worthy to share with them. I think it also would be worthy of doing some comprehension testing around whatever is communicated.

I couldn't tell if it was in the label or not, so I'm just going to say it. I think it's also important to include risks in the pregnant or postpartum period for comparison. And of course add the FDA's new study which isn't in there. And I would agree with the other comment mentioned previously that we want to be careful that this isn't a litany of the literature. So whether or not you can just include now the FDA study or just include the regulatory based studies as opposed to every study in the literature would be something to think about, maybe cite other studies but not confuse it with listing 10 studies like we had to sort through.

Mark Woods: Woods. Voted no and I would just echo again what Dr. Morrato said. We heard in the open hearing session today that the message is not getting through to patients and so improvements in the product labeling for physicians that would then be reflected in what we give patients I think would be great.

Valerie Montgomery Rice: Montgomery Rice. I voted no. I think we can do a much better job than the labels that I have seen. I think the information is too confusing. I think patients and doctors do a lot better with understanding the absolute risk and so I definitely think we can do a better job.

Julia Johnson: Johnson. I voted yes mainly because I think we need to have a little bit more data. I really do think it needs to be completely redone in the future but I would like to have more information from the FDA study so that we can communicate that effectively to patients. I hope we can do that in a fairly short order in looking at that data in more detail so that we can communicate that effectively to patients. I do agree that we need to make it easier to read.

Michele Orza: Orza. I voted no. I feel like we're shirking our responsibility to simply kind of throw the studies in there and lay them out and what we're saying is we can't make sense of it and we're expecting somehow that clinicians and patients will be able to do what we're not able to do. I think the current -- the thing we saw on the slide is -- because of the order in which things are presented, and because the FDA study is missing, and because there's no criticism of the positive studies and there's lots of criticism of the negative studies, essentially says ignore the negative studies.

I think in terms of the specific improvements we were asked about, I think it would be a good idea to have a version of figure, the figure that's on Page 8, which is a very nice graphic that conveys the relative effectiveness of different methods, to have a similar kind of graphic that conveys the spectrum of risk across different, in this case, different

pills. In terms of interpreting the findings better, I do think there does need to be something more synthetic that presents the findings across all of these studies, even if it's just a range.

And in terms of other things that we might want to add, I didn't see anything about long haul flights and I thought that the evidence had kind of evolved to the point where we should be giving people a heads up about that. And then in terms of if there's anything you can do beyond the labeling, if there's a possibility of a REMS or of controlling direct-to-consumer advertising, or in terms of rethinking the indications so that maybe this is a second line treatment.

Julia Johnson: Dr. Bockman?

Richard Bockman: Bockman. And I voted no. Clearly the wording is inadequate. It's not complete, period. The only comment I want to make is what could make these warnings better, and I think what we need is more graphic language of what the adverse events actually are. I think we need to say that things like deep vein thrombosis can cause permanent injury to a limb and that should be very clear. And I think we need to say things like pulmonary embolism can result in death or lifetime incapacities. And I just think that the adverse events have to be made graphic so that physician and patients are aware of what the consequences of these things are.

Kathleen Hoeger: Hoeger. I voted no. I agree that we need to be more explicit with all of the studies and would echo the comments relating to a tabular form. I think this is much easier for patients and physicians to compare. And as well, put in the pregnancy risks associated.

John Kittelson: Kittelson. I voted yes. I don't think we have enough information to quantify risk yet for summary sorts of statements. I would echo some of the comments of Dr. Johnson (inaudible).

Melissa Gilliam: Gilliam. I voted no. I'm noticing that no one likes the label but some are voting no and some are voting yes so maybe the question is a little confusing. But I think the label is too complicated. It doesn't include all the studies. I noticed when Dr. Lukes talked about how she counseled her patients it sounded complicated and hard to follow. So I think what we want to do is try to give prescribing physicians more information. But I do want to qualify; I think we're not differentiating between initiation and continuation.

And when we talk about things like is this a pill that should no longer be on the market, people are already on it and happy and have been on it for years. I don't think this conversation affects them. So I think we want to be careful in the way that we roll out these types of comments because it can be hard for people to find a pill and I don't want to suggest that there's somehow a new risk that wasn't there now that they've been on it for years. So I think the label needs work but I think we have to be very careful that we're not giving a message that suddenly this pill you've been happy on is somehow threatening to you.

Bart Clarke: Clarke. I voted yes because I think the uncertainty that's written in the label now does express the uncertainty that we face. There are studies not mentioned in there and I think the Canadian label did a nice job describing some of the additional studies. But I voted yes because I think the uncertainty is there. As a physician, I deal with uncertainty every day with every patient and there's no way to predict, until it happens, what's going to happen in any of these people. The label should reflect that. To have a simple statement that really applies to all situations I think is very difficult to write.

Diane Aronson: Aronson. I voted no just considering that it is very hard to predict the idiopathic kinds of events but just listening to the powerful presentations from the patients and families today about how the label potentially had failed them, the current label. I also would agree with Dr. Gardner about something visibly that would be easier to analyze. And I'm wondering if in studies, in labels it ever lists funders, like who funded particular studies. And then also Dr. Bockman's comments about the impact and quality of life, not only the death issue but how devastating the risk can be.

Dale Stovall: Stovall. I voted yes primarily because I don't think I have a better answer than what we have in there. I think it is true that it's somewhat vague. We don't have precise numbers, precise data. I think trying to put that in there would not be appropriate. And I'm not really sure it would make a big difference for patients either. I don't know if they can use information to say that this goes from three in 10,000 to eight or nine or ten in 10,000. What does that mean to somebody? You know, I think it's very difficult as an individual and as a patient to make decisions based on that kind of information. I don't think patients do it very well. I mean that was mentioned earlier that they don't understand, it's not easy to understand that kind of risk assessment and management.

And I think it's the clinician, I think as Dr. Clarke said a moment ago, really it's the clinician that needs to understand this information as best as she or he can and then to communicate that information to the patient. I don't think a patient takes (inaudible) now there may be some way we can have a patient insert or information that they have, maybe even signing some kind of consent. I think that's been tried. I know there are places where a patient signs and says yes, I understand this increases my risk for a DVT, et cetera. But I think to think that we can explain and educate them completely in a handout is not realistic.

Geri Hewitt: Dr. Hewitt. I voted no and the reason I voted no, I think some of the new information should be included. And I echo that I think it's one of the hardest things I do as a clinician is to explain to patients the difference between population risk and their risk as an individual. I think that's very difficult to do and I think a lot of clinicians do so struggle with interpreting epidemiologic data. So I think anything we can do to enhance the clinician's understanding of this information, which would include I think articles they can read on their own or generally a statement that the risk, relative risk may be increased however the absolute risk remains small. I think if we can empower the clinicians to be comfortable with that information it might help them to communicate those risks to the patient.

Eve Espey: Espey. I voted no for the reasons that other people have discussed.

Julia Johnson: Well I would like to most sincerely thank the advisory committee for all of the information that you've provided. I would like to thank you too for your patience in our adjustment with the voting. I think the information that you've provided to the FDA has been invaluable. I do need you to stay in the room with me for just a moment. We can allow all the visitors, however, to go. I would also like to offer my thanks to the sponsors and my special thanks to the FDA, including Dr. Monroe for all of their guidance in terms of this advisory committee meeting. And everyone have a good evening but stay in your seats for just a moment.